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Although this document is principally concerned with the health and welfare effects of lead, other scientific data are presented and evaluated in order to provide a better understanding of this pollutant in the environment. To this end, the document includes chapters that discuss: the chemistry and physics of the pollutant; analytical levels; atmospheric chemistry and dispersion modeling; effects on vegetation; and respiratory, physiological, toxicological, clinical and epidemiological aspects of human exposure.

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LIST OF ABBREVIATIONS

AAS	Atomic absorption spectrometry
Ach	Acetylcholine
ACTH	Adrenocorticotrophic hormone
ADCC	Antibody-dependent cell-mediated cytotoxicity
ADP/O ratio	Adenosine diphosphate/oxygen ratio
AIDS	Acquired immune deficiency syndrome
AIHA	American Industrial Hygiene Association
AII	Angiotensin II
ALA	Aminolevulinic acid
ALA-D	Aminolevulinic acid dehydrase
ALA-S	Aminolevulinic acid synthetase
ALA-U	Aminolevulinic acid in urine
APDC	Ammonium pyrrolidine-dithiocarbamate
APHA	American Public Health Association
ASTM	Amercian Society for Testing and Materials
ASV	Anodic stripping voltammetry
ATP	Adenosine triphosphate
B-cells	Bone marrow-derived lymphocytes
Ba	Barium
BAL	British anti-Lewisite (AKA dimercaprol)
BAP	benzo(a)pyrene
BSA	Bovine serum albumin
BUN	Blood serum urea nitrogen
BW	Body weight
C.V.	Coefficient of variation
CaBP	Calcium binding protein
CaEDTA	Calcium ethylenediaminetetraacetate
$CaNa_2EDTA$	Calcium sodium ethylenediaminetetraacetate
CBD	Central business district
Cd	Cadmium
CDC	Centers for Disease Control
CEC	Cation exchange capacity
CEH	Center for Environmental Health
CFR	reference method
CMP	Cytidine monophosphate
CNS	Central nervous system
CO	Carbon monoxide
COHb	Carboxyhemoglobin
CPB	Competitive protein binding
CP-U	Urinary coproporphyrin
C_{pah}	plasma clearance of p-aminohippuric acid
Cu	Copper
D.F.	Degrees of freedom
DA	Dopamine
δ-ALA	delta-aminolevulinic acid
DCMU	[3-(3,4-dichlorophenyl)-1,1-dimethylurea
DPP	Differential pulse polarography
DNA	Deoxyribonucleic acid
DTH	Delayed-type hypersensitivity
EEC	European Economic Community
EEG	Electroencephalogram
EMC	Encephalomyocarditis

LIST OF ABBREVIATIONS (continued).

EP	Erythrocyte protoporphyrin
EPA	U.S. Environmental Protection Agency
FA	Fulvic acid
FDA	Food and Drug Administration
Fe	Iron
FEP	Free erythrocyte protoporphyrin
FY	Fiscal year
G.M.	Grand mean
G-6-PD	Glucose-6-phosphate dehydrogenase
GABA	Gamma-aminobutyric acid
GALT	Gut-associated lymphoid tissue
GC	Gas chromatography
GFR	Glomerular filtration rate
GI	Gastrointestinal
HA	Humic acid
HANES I	Health Assessment and Nutrition Evaluation Survey
Hb	Hemoglobin
Hg	Mercury
hi-vol	High-volume air sampler
HPLC	High-performance liquid chromatography
i.m.	Intramuscular (method of injection)
i.p.	Intraperitoneally (method of injection)
i.v.	Intravenously (method of injection)
IAA	Indol-3-ylacetic acid
IARC	International Agency for Research on Cancer
ICD	International classification of diseases
ICP	Inductively coupled plasma emission spectroscopy
IDMS	Isotope dilution mass spectrometry
IF	Interferon
ILE	Isotopic Lead Experiment (Italy)
IRPC	International Radiological Protection Commission
K	Potassium
LDH-X	Lactate dehydrogenase isoenzyme x
LC_{50}	Lethyl concentration (50 percent)
LD_{50}	Lethal dose (50 percent)
LH	Luteinizing hormone
LIPO	Laboratory Improvement Program Office
ln	Natural logarithm
LPS	Lipopolysaccharide
LRT	Long range transport
mRNA	Messenger ribonucleic acid
ME	Mercaptoethanol
MEPP	Miniature end-plate potential
MES	Maximal electroshock seizure
MeV	Mega-electron volts
MLC	Mixed lymphocyte culture
MMD	Mass median diameter
MMAD	Mass median aerodynamic diameter
Mn	Manganese
MND	Motor neuron disease
MSV	Moloney sarcoma virus
MTD	Maximum tolerated dose

LIST OF ABBREVIATIONS (continued).

n	Number of subjects or observations
N/A	Not Available
NA	Not Applicable
NAAQS	National ambient air quality standards
NAD	Nicotinamide Adenine Dinucleotide
NADB	National Aerometric Data Bank
NAMS	National Air Monitoring Station
NAS	National Academy of Sciences
NASN	National Air Surveillance Network
NBS	National Bureau of Standards
NE	Norepinephrine
NFAN	National Filter Analysis Network
NFR-82	Nutrition Foundation Report of 1982
NHANES II	National Health Assessment and Nutritional Evaluation Survey II
Ni	Nickel
NTA	Nitrilotriacetonitrile
OSHA	Occupational Safety and Health Administration
P	Phosphorus
p	Significance symbol
PAH	Para-aminohippuric acid
Pb	Lead
PBA	Air lead
$Pb(Ac)_2$	Lead acetate
PbB	concentration of lead in blood
PbBrCl	Lead (II) bromochloride
PBG	Porphobilinogen
PFC	Plaque-forming cells
pH	Measure of acidity
PHA	Phytohemagglutinin
PHZ	Polyacrylamide-hydrous-zirconia
PIXE	Proton-induced X-ray emissions
PMN	Polymorphonuclear leukocytes
PND	Post-natal day
PNS	Peripheral nervous system
P.O.	Per os (orally)
ppm	Parts per million
PRA	Plasma renin activity
PRS	Plasma renin substrate
PWM	Pokeweed mitogen
Py5N	Pyrimide-5'-nucleotidase
RBC	Red blood cell; erythrocyte
RBF	Renal blood flow
RCR	Respiratory control ratios/rates
redox	Oxidation-reduction potential
RES	Reticuloendothelial system
RLV	Rauscher leukemia virus
RNA	Ribonucleic acid
S-HT	Serotonin
SA-7	Simian adenovirus
S.C.	Subcutaneously (method of injection)
scm	Standard cubic meter
S.D.	Standard deviation

LIST OF ABBREVIATIONS (continued).

SDS	Sodium dodecyl sulfate
S.E.M.	Standard error of the mean
SES	Socioeconomic status
SGOT	Serum glutamic oxaloacetic transaminase
sIg	Surface immunoglobulin
SLAMS	State and local air monitoring stations
SMR	Standardized mortality ratio
Sr	Strontium
SRBC	Sheep red blood cells
SRMs	Standard reference materials
STEL	Short-term exposure limit
SW voltage	Slow-wave voltage
T-cells	Thymus-derived lymphocytes
t-tests	Tests of significance
TBL	Tri-n-butyl lead
TEA	Tetraethyl-ammonium
TEL	Tetraethyllead
TIBC	Total iron binding capacity
TML	Tetramethyllead
TMLC	Tetramethyllead chloride
TSH	Thyroid-stimulating hormone
TSP	Total suspended particulate
U.K.	United Kingdom
UMP	Uridine monophosphate
USPHS	U.S. Public Health Service
VA	Veterans Administration
V_d	Deposition velocity
VER	Visual evoked response
WHO	World Health Organization
XRF	X-Ray fluorescence
X^2	Chi squared
Zn	Zinc
ZPP	Erythrocyte zinc protoporphyrin

MEASUREMENT ABBREVIATIONS

dl	deciliter
ft	feet
g	gram
g/gal	gram/gallon
g/ha·mo	gram/hectare·month
km/hr	kilometer/hour
l/min	liter/minute
mg/km	milligram/kilometer
$\mu g/m^3$	microgram/cubic meter
mm	millimeter
μm	micrometer
μmol	micromole
ng/cm^2	nanograms/square centimeter
nm	nanometer

LIST OF ABBREVIATIONS (continued).

nM	nanomole
sec	second
t	tons

GLOSSARY VOLUME III

aerosol - a suspension of liquid or solid particles in a gas

BAL (British Anti-Lewisite) - a chelating agent often used in the treatment of metal toxicity

biliary clearance - an excretion route involving movement of an agent through bile into the GI tract

Brownian diffusion - the random movement of microscopic particles

"chelatable" or systemically active zinc - fraction of body's zinc store available or accessible to removal by a zinc-binding agent

chi-square goodness-of-fit tests - made to determine how well the observed data fit a specified model, these tests usually are approximately distributed as a chi-square variable

first-order kinetics - a kinetic process whose rate is proportional to the concentration of the species undergoing change

geochronometry - determination of the age of geological materials

hematocrit - the percentage of the volume of a blood sample occupied by cells

intraperitoneal - within the body cavity

likelihood function - a relative measure of the fit of observed data to a specified model. In some special cases it is equivalent to the sum of squares function used in least squares analysis.

mass median aerodynamic diameter (MMAD) - the aerodynamic diameter (in μm) at which half the mass of particles in an aerosol is associated with values below and half above

multiple regression analysis - the fitting of a single dependent variable to a linear combination of independent variables using least squares analysis

plumburesis - lead excreted in urine

R^2 - this statistic, often called the multiple R squared, measures the proportion of total variation explained. A value near 1 means that nearly all of the variation is explained, whereas a value near zero means that almost none of the variation is explained.

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9. QUANTITATIVE EVALUATION OF LEAD AND BIOCHEMICAL INDICES OF LEAD EXPOSURE IN PHYSIOLOGICAL MEDIA

9.1 INTRODUCTION

To understand the effects of an agent on an organism and, in particular, to formulate statements of dose-effect relationships, one must be able to assess quantitatively the organism's degree of exposure to the substance. In the case of lead, internal biologically based measures provide a more accurate indication of exposure than do external measures such as ambient air concentrations. Internal measures may be either direct--e.g., the level of lead in a biological medium such as blood, calcified tissue, etc.--or indirect--e.g., the level of some biochemical parameter or "indicator" closely associated with internal lead exposure. This chapter examines the merits and weaknesses of various measurement methods as they are currently used to assess lead exposure.

Quantitative analysis involves a number of discrete steps, all of which are important contributors to the quality of the final result: (1) sample collection and transmission to the laboratory; (2) laboratory manipulation of samples, physically and chemically, before analysis by instruments; (3) instrumental analysis and quantitative measurement; and (4) establishment of relevant criteria for accuracy and precision, namely, internal and external quality assurance checks. Each of these steps is discussed in this chapter in relation to the measurement of lead exposure.

Clearly, the definition of "satisfactory analytical method" for lead has changed over the years, paralleling (1) the evolution of more sophisticated instrumentation and procedures, (2) a greater awareness of such factors as background contamination and loss of the element from samples, and (3) development of new statistical methods to analyze data. For example, current methods of lead analysis, such as anodic stripping voltammetry, background-corrected atomic absorption spectrometry, and particularly isotope-dilution mass spectrometry, are more sensitive and specific than the older classical approaches. Increasing use of the newer methods would tend to result in lower lead values being reported for a given sample. Whether this trend in analytical improvement can be isolated from other variables such as temporal changes in exposure is another matter.

Because lead is ubiquitously distributed as a contaminant, the constraints (i.e., ultraclean, ultra-trace analysis) placed upon a laboratory attempting analysis of geochemical samples of pristine origin, or of extremely low lead levels in biological samples such as plasma, are quite severe (Patterson, 1980). Very few laboratories can credibly claim such capability.

Ideally, similar standards of quality should be adhered to across the rest of the analytical spectrum. With many clinical, epidemiological, and experimental studies, however, these standards may be unrealistic given the practical limitations and objectives of the studies. Laboratory performance is but one part of the quality equation; the problems of sampling are equally important but less subject to tight control. The necessity of rapidly obtaining a blood sample in cases of suspected lead poisoning, or of collecting hundreds or thousands of blood samples in urban populations, limits the number of sampling safeguards that can be realistically achieved. Sampling in this context will always be accompanied by a certain amount of analytical "suspicion." Furthermore, a certain amount of biological lead analysis data is employed for comparative purposes, as in experimental studies concerned with the relative increase in tissue burden of lead associated with increases in doses or severity of effects. In addition, any major compromise of an analytical protocol may be statistically discernible. Thus, analysis of biological media for lead must be done under protocols that minimize the risk of inaccuracy. Specific accuracy and precision characteristics of a method in a particular report should be noted to permit some judgment on the part of the reader about the influence of methodology on the reported results.

The choice of measurement method and medium for analysis is dictated both by the type of information desired and by technical or logistical considerations. As noted elsewhere in this document, whole blood lead reflects recent or continuing exposure, whereas lead in mineralized tissue, such as deciduous teeth, reflects an exposure period of months and years. While urine lead values are not particularly good correlates of lead exposure under steady-state conditions in populations at large, such measurements may be of considerable clinical value. In acquiring blood samples, the choice of venipuncture or finger puncture will be governed by such factors as cost and feasibility, contamination risk, and the biological quality of the sample. The use of biological indicators that strongly correlate with lead burden may be more desirable, since they provide evidence of actual response and, together with blood lead data, provide a less risky diagnostic tool for assessing lead exposure.

9.2 DETERMINATIONS OF LEAD IN BIOLOGICAL MEDIA

9.2.1 Sampling and Sample Handling Procedures for Lead in Biological Media

Lead analysis in biological media requires careful sample collection and handling for two reasons: (1) lead occurs at trace levels in most indicators of subject exposure, even under conditions of high lead exposure; and (2) such samples must be obtained against a backdrop of pervasive contamination, the full extent of which may still be unrecognized by many laboratories.

The reports of Speecke et al. (1976), Patterson and Settle (1976), Murphy (1976), Berman (1976), and Settle and Patterson (1980) review detailed aspects of the problems of sampling and subsequent sample handling in the laboratory. These reports indicate that the normal precautions taken during sampling (detailed below for clinical and epidemiological studies) should not be considered absolute, but rather as what is practical and feasible. They further indicate that the inherent sensitivity or accuracy of a given method or instrument may be less of a determining factor in the overall analysis than the quality of sample collection and handling.

9.2.1.1 Blood Sampling. Samples for blood lead determination may be collected by venipuncture (venous blood) or fingertip puncture (capillary blood). Collection of capillary versus venous blood is usually decided by a number of factors, including the feasibility of obtaining samples during the screening of many subjects and the difficulty of securing subject compliance, particularly in the case of children and their parents. Furthermore, capillary blood may be collected as discrete quantities in small-volume capillary tubes or as spots on filter paper disks. With capillary tubes, obtaining good mixing with anticoagulant to avoid clotting is important, as is the problem of lead contamination of the tube. The use of filter paper requires the selection of paper with uniform composition, low lead content, and uniform blood dispersal characteristics.

Whether venous or capillary blood is collected, much care must be exercised in cleaning the site before puncture as well as in selecting lead-free receiving containers. Cooke et al. (1974) employed vigorous scrubbing with a low-lead soap solution and rinsing with deionized water, while Marcus et al. (1975) carried out preliminary cleaning with an ethanolic citric acid solution followed by rinsing with 70-percent ethanol. Vigor in cleaning the puncture site is probably as important as the choice of any particular cleaning agent. Marcus et al. (1977) have noted that in one procedure for puncture site preparation, where the site is covered with wet paper towels, contamination will occur if the paper towels are made from recycled paper. Recycled paper retains a significant amount of lead.

In theory, capillary and venous blood lead levels should be virtually identical. However, the literature indicates that some differences, which mainly reflect sampling problems, do arise in the case of capillary blood. A given amount of contaminant has a greater impact on a 100-μl fingerstick sample than on a 5-ml sample of venous blood. Finger-coating techniques may reduce some of the contamination (Mitchell et al., 1974). An additional problem is the presence of lead in the anticoagulants used to coat capillary tubes. Also, lower values of capillary versus venous blood lead may reflect "dilution" of the sample by extracellular fluid from excessive compression of the puncture site. When Joselow and Bogden (1972) compared a method using finger puncture and spotting onto filter paper with a procedure using venous blood and Hessel's procedure (1968) for flame atomic absorption spectrometry (see Section 9.2.2.1), they obtained a correlation coefficient of $r = 0.9$ (range, 20-46 μg/dl). Similarly, Cooke et al. (1974) found an r value of 0.8 (no range given), while Mitchell et al. (1974) obtained a value of 0.92 (10-92 μg/dl). Mahaffey et al. (1979) found that capillary blood levels in a comparison test were approximately 20 percent higher than corresponding venous blood levels in the same subjects, presumably reflecting sample contamination. Similar elevations have been described by DeSilva and Donnan (1980). Carter (1978) has found that blood samples with lower hemoglobin levels may spread onto filter paper differently from normal hemoglobin samples, requiring correction in quantification to obtain reliable values. This complication should be kept in mind when considering children, who are frequently prone to iron-deficiency anemia.

The relative freedom of the blood container from interior surface lead and the presence of lead in the anticoagulant to be added to the blood are important considerations in venous sampling. For studies focusing on "normal" ranges, such tubes may add some lead to blood and still meet certification requirements. The "low-lead" heparinized blood tubes commercially available (blue stopper Vacutainer, Becton-Dickinson) were found to contribute less than 0.2 μg/dl to whole blood samples (Rabinowitz and Needleman, 1982). Nackowski et al. (1977) surveyed a large variety of commercially available blood tubes for lead and other metal contamination. Lead uptake by blood over time from the various tubes was minimal with the "low-lead" Vacutainer tubes and with all but four of the other tube types. In the large survey of Mahaffey et al. (1979), 5-ml Monoject (Sherwood) or 7-ml lavender-top Vacutainer (Becton-Dickinson) tubes were satisfactory. However, when more precision is needed, tubes are best recleaned in the laboratory and lead-free anticoagulant added (although this would be less convenient for sampling efficiency than the commercial tubes). In addition, blank levels for every batch of samples should be verified.

9.2.1.2 Urine Sampling. Urine samples require collection using lead-free containers and caps as well as the addition of a low-lead bactericide if samples are to be stored. While not always feasible, 24-hr samples should be obtained because they level out any effect of variation in excretion over time. If spot sampling is done, lead levels should be expressed per unit creatinine, or corrected for a constant specific gravity, if greater than 1.010.

9.2.1.3 Hair Sampling. The usefulness of hair lead analysis depends on the manner of sampling. Hair samples should be removed from subjects by a consistent method, either by a predetermined length measured from the skin or by using the entire hair. Hair should be placed in air-tight containers for shipment or storage. For segmental analysis, the entire hair length is required.

9.2.1.4 Mineralized Tissue. An important consideration in deciduous tooth collection is consistency in the type of teeth collected from various subjects. Fosse and Justesen (1978) reported no difference in lead content between molars and incisors, and Chatman and Wilson (1975) reported comparable whole tooth levels for cuspids, incisors, and molars. On the other hand, Mackie et al. (1977) and Lockeretz (1975) noted levels varying with tooth type, with a statistically significant difference (Mackie et al., 1977) between second molars (lowest levels) and incisors (highest levels). That the former two studies found rather low overall lead levels across groups, while Mackie et al. (1977) reported higher values, suggests that dentition differences in lead content may be magnified at relatively higher levels of exposure. Delves et al. (1982), comparing pairs of central incisors or pairs of central and lateral incisors from the same child, found that lead content may even vary within a specific type of tooth. These data suggest the desirability of acquiring two teeth per subject to get an average lead value.

Teeth containing fillings or extensive decay are best eliminated from analysis. Mackie et al. (1977) discarded decayed teeth if the extent of decay exceeded approximately 30 percent.

9.2.1.5 Sample Handling in the Laboratory. The effect of storage on lead content is a potential problem with blood samples. During storage, dilute aqueous solutions of lead surrender a sizable portion of the lead content to the container surface, whether glass or plastic, unless the sample is acidified (Issaq and Zielinski, 1974; Unger and Green, 1977). Whether there is a comparable effect, or comparable extent of such an effect, with blood is not clear. Unger and Green (1977) claim that lead loss from blood to containers parallels that seen with aqueous solutions, but their data do not support this assertion. Moore and Meredith (1977) used isotopic lead spiking (^{203}Pb) with and without carrier in various containers at differing temperatures to monitor lead stability in blood over time. The only material loss occurred with soda glass at room temperature after 16 days. Nackowski et al. (1977) found that "low-lead" blood tubes, while quite satisfactory in terms of sample contamination, began to show transfer of lead to the container wall after 4 days. Méranger et al. (1981) studied movement of lead, spiked to various levels, to containers of various composition as a function of temperature and time. In all cases, reported lead loss to containers was significant. However, problems exist with the above reports. Spiked samples probably are not incorporated into the same biochemical environment as lead inserted *in vivo*. Also, Nackowski et al. (1977) did not indicate whether the blood samples were kept frozen or refrigerated between testing intervals. Mitchell et al. (1972) found that the effect of blood storage depends on the method of analysis, with lower recoveries of lead from aged blood using the Hessel (1968) method.

Lerner (1975) collected blood samples (35 originally) from a single subject into lead-free tubes and, after freezing, forwarded them in blind fashion to a certified testing laboratory over a period of 9 months. Four samples were lost, and one was rejected as grossly contaminated (4 standard deviations from mean). Of the remaining 30 samples, the mean was 18.3 µg/dl with a standard deviation (S.D.) of 3.9. The analytical method had a precision of ±3.5 µg/dl (S.D. = 1) at normal levels of lead, suggesting that the overall stability of the samples' lead content was good. Boone et al. (1979) reported that samples frozen for periods of less than 1 year showed no effect of storage, while Piscator (1982) noted no change in low levels (<10 µg/dl) when samples were stored at -20°C for 6 months. Based on the above data, blood samples to be stored for any period of time should be frozen rather than refrigerated, with care taken to prevent breaking the tube during freezing. Teeth and hair samples, when stored in containers to minimize contamination, are indefinitely stable.

The actual site of analysis should be as free from lead as possible. Given the limited availability of an "ultra-clean" facility such as that described by Patterson and Settle (1976), the next desirable level of laboratory is the "Class 100" facility, in which fewer than 100 airborne particles are greater than 0.5 µm in diameter. These facilities employ high-efficiency particulate air filtering and laminar air flow (with movement away from sample handling areas). Totally inert surfaces in the working area and an antechamber for removing contaminated clothes, appliance cleaning, etc., are other necessary features.

All plastic and glass ware coming into contact with samples should be cleaned rigorously and stored away from dust contact, and materials such as ashing vessels should permit minimal lead leaching. In this regard, Teflon or quartz ware is preferable to other plastics or borosilicate glass (Patterson and Settle, 1976).

Reagents, particularly for chemical degradation of biological samples, should be both certified and periodically tested for quality. Several commercial grades of reagents are available, although precise work may require doubly purified materials from the National Bureau of Standards (NBS). These reagents should be stored with a minimum of surface contamination around the top of the containers.

For a more detailed discussion of appropriate laboratory practices, the reader may consult LaFleur (1976).

9.2.2 Methods of Lead Analysis

Detailed technical discussion of the array of instruments available to measure lead in blood and other media is outside the scope of this chapter (see Chapter 4). This discussion is structured more appropriately to those aspects of methodology dealing with relative sensitivity, specificity, accuracy, and precision. While acceptance of international standardized

(SI) units for expressing lead levels in various media is increasing, units familiar to clinicians and epidemiologists will be used here. (To convert μg Pb/dl blood to SI units [μmoles/liter], multiply by 0.048.)

Many reports over the years have purported to offer satisfactory analysis of lead in biological media, but in fact have shown rather meager adherence to criteria for accuracy and precision or have shown a lack of demonstrable utility across a wide spectrum of analytical applications. Therefore, discussion in this section is confined to "definitive" and reference methods for lead analysis, except for a brief treatment of the traditional but now widely supplanted colorimetric method.

Using the definition of Cali and Reed (1976), a definitive method is one in which all major or significant parameters are related by solid evidence to the absolute mass of the element with a high degree of confidence. A reference method, by contrast, is one of demonstrated accuracy, validated by a definitive method, and arrived at by consensus through performance testing by a number of different laboratories. In the case of lead in biological media, the definitive method is isotope-dilution mass spectrometry (IDMS). IDMS is so accurate because all manipulations are on a weight basis involving simple procedures. The measurements entail only ratios and not the absolute determinations of the isotopes involved, which greatly reduces instrumental corrections or errors. No interferences occur from sample matrix or other elements, and the method does not depend on recovery. Reproducible results to a precision of one part in 10^4 or 10^5 are routine with specially designed instruments.

In terms of reference methods for lead in biological media, such a label is commonly attached to atomic absorption spectrometry (AAS) in its various instrumentation/ methodology configurations and to the electrochemical technique, anodic stripping voltammetry (ASV). These have been termed reference methods insofar as their precision and accuracy can be verified or calibrated against IDMS.

Other methods that are recognized for general trace-metal analysis are not fully applicable to biological lead or have inherent shortcomings. X-ray fluorescence analysis lacks the requisite sensitivity for media with low lead content, and the associated sample preparation may present a high contamination risk. A notable exception may be X-ray fluorescence analysis of teeth or bone _in situ_ as discussed below. Neutron-activation analysis is the method of choice with many elements, but it is not technically feasible for lead analysis because of the absence of long-lived isotopes.

9.2.2.1 _Lead Analysis in Whole Blood_. The first generally accepted technique for quantifying lead in whole blood and other biological media was a colorimetric method that involved spectrophotometric measurement based on the binding of lead to a chromogenic agent to yield a chromophoric complex. The complexing agent has typically been dithizone, 1,5-diphenylthiocarbazone, yielding a lead complex that is spectrally measured at 510 nm.

Two variations of the spectrophotometric technique used when measuring low levels of lead have been the procedures of the U.S. Public Health Service (USPHS) (National Academy of Sciences, 1972) and of the American Public Health Association (APHA) (1955). In both, venous blood or urine is wet ashed using concentrated nitric acid of low lead content followed by adjustment of the ash with hydroxylamine and sodium citrate to a pH of 9-10. Cyanide ion is added and the solution extracted with dithizone in chloroform. Back extraction removes the lead into dilute nitric acid; the acid layer is treated with ammonia, then cyanide, and re-extracted with dithizone in chloroform. The extracts are read in a spectrophotometer at 510 nm. Bismuth interference is handled (APHA variation) by removal with dithizone at pH 3.4. According to Lerner (1975), the analytical precision in the "normal" range is about ±3.5 μg/dl (S.D. = 1), using 5 ml of sample.

The most accurate and precise method for lead measurement in blood is IDMS. As typified by the report of Machlan et al. (1976), whole blood samples are accurately weighed, and a weighed aliquot of ^{206}Pb-enriched isotope solution is added. After sample decomposition with ultra-pure nitric and perchloric acids, samples are evaporated, residues are taken up in dilute lead-free hydrochloric acid (HCl), and lead is isolated using anion-exchange columns. Column eluates are evaporated with the above acids, and lead is deposited onto high-purity platinum wire from dilute perchloric acid. The ^{206}Pb/^{208}Pb ratio is then determined by thermal ionization mass spectrometry. Samples without added isotope and reagent blanks are also carried through the procedure. In terms of precision, the 95-percent confidence level for lead samples overall is within 0.15 percent. Because of the expense incurred by the requirements for operator expertise, the amount of time involved, and the high standard of laboratory cleanliness, IDMS is mainly of practical value in the development of standard reference materials and for the verification of other analytical methods.

AAS is widely used for lead measurements in whole blood, with sample analysis involving analysis of venous blood with chemical degradation, analysis of liquid samples with or without degradation, and samples applied to filter paper. It is thus the most flexible for samples already collected or subject to manipulation. By means of flame or electrothermal excitation, ionic lead in a matrix is first vaporized and then converted to the atomic state, followed by resonance absorption from either a hollow cathode or electrodeless discharge lamp generating lead absorption lines at 217.0 and 283.3 nm. After monochrometer separation and photomultiplier enhancement of the differential signal, lead content is measured electronically.

The earliest methods of AAS analysis involved the aspiration of ashed blood samples into a flame, usually subsequent to extraction into an organic solvent, to enhance sensitivity by preconcentration. Some methods did not involve digestion steps prior to solvent extraction

(Kopito et al., 1974). Of these various flame AAS methods, Hessel's (1968) technique continues to be used with some frequency.

Currently, lead measurement in blood by AAS employs several different methods that permit greater sensitivity, precision, and economy of sample and time. The flame method of Delves (1970), called the "Delves cup" procedure, usually involves delivery of discrete small samples (≤100 μl) of unmodified whole blood to nickel cups, with subsequent drying and peroxide decomposition of organic content before positioning in the flame. The marked enhancement of sensitivity over conventional flame aspiration results from immediate, total consumption of the sample and generation of a localized population of atoms. In addition to discrete blood volumes, blood-containing filter paper disks have been used (Joselow and Bogden, 1972; Cernik and Sayers, 1971; Piomelli et al., 1980). Among the several modifications of the Delves method are that of Ediger and Coleman (1972), in which dried blood samples in the cups are preignited to destroy organic matter by placement near the flame in a precise, repeatable manner, and the variation of Barthel et al. (1973), in which blood samples are mixed with dilute nitric acid in the cups followed by drying in an oven at 200°C and charring at 450°C on a hot plate. A number of laboratories eschew even these modifications and follow dispensing and drying with direct placement of the cup into the flame (e.g., Mitchell et al., 1974). The Delves cup procedure may require correction for background spectral interference. This correction is usually achieved using instrumentation equipped at a nonresonance absorption line. While the 217.0-nm line of lead is less subject to such interference, precise work is best done with correction. This method as applied to whole blood lead appears to have an operational sensitivity down to 1.0 μg Pb/dl, or somewhat below when competently employed, and a relative precision of approximately 5 percent in the range of levels encountered in the United States.

AAS methods using electrothermal (furnace) excitation in lieu of a flame can be approximately tenfold more sensitive than the Delves procedure. A number of reports describing whole blood lead analysis have appeared in the literature (Lawrence, 1982, 1983). Because of increased sensitivity, the "flameless" AAS technique permits the use of small blood volumes (1-5 μl) with samples undergoing drying and dry ashing *in situ*. Physicochemical and spectral interferences are inherently severe with this approach, requiring careful background correction. In one flameless AAS configuration, background correction exploits the Zeeman effect, where correction is made at the specific absorption line of the element and not over a band-pass region, as is the case with the deuterium arc. While control of background interference up to 1.5 molecular absorbance is claimed with the Zeeman system (Koizumi and Yasuda, 1976), employing charring before atomization is technically preferable. Hinderberger et al. (1981) used dilute ammonium phosphate solution to minimize chemical interference in their furnace AAS method.

Precision can be a problem in the flameless technique unless careful attention is paid to the problem of sample diffusibility over and into the graphite matrix of the receiving receptacle (tube, cup, or rod). With the use of diluted samples and larger applied volumes, the relative precision of this method can approach that of the Delves technique (Delves, 1977).

In addition to the various AAS methods noted above, electrochemical techniques have been applied to blood lead analysis. Electrochemical methods, in theory, differ from AAS methods in that the latter are "concentration" methods regardless of sample volumes available, while electrochemical analysis involves bulk consumption of sample and hence would have infinite sensitivity, given an infinite sample volume. This intrinsic property is of little practical advantage given usual limits of sample volume, instrumentation design, and blanks.

The most widely used electrochemical method for lead measurement in whole blood and other biological media is ASV, which is also probably the most sensitive because it involves an electrochemical preconcentration (deposition) step in the analysis (Matson and Roe, 1966; Matson et al., 1971). In this method, samples such as whole blood (50-100 µl) are preferably, but not commonly, wet ashed and reconstituted in dilute acid or made electro-available with metal exchange reagents. Using freshly prepared composite electrodes of mercury film deposited on carbon, lead is plated out from the solution for a specific amount of time and at a selected negative voltage. The plated lead is then reoxidized in the course of anodic sweeping, generating a current peak that may be recorded on a chart or displayed on commercial instruments as units of concentration (µg/dl).

One alternative to the time and space demands of wet ashing blood samples is the use of metal exchange reagents that displace lead from binding sites in blood by competitive binding (Morrell and Giridhar, 1976; Lee and Méranger, 1980). In one commercial preparation, this reagent consists of a solution of calcium, chromium, and mercuric ions. Use of the metal exchange reagent adds a chemical step that must be carefully controlled for full recovery of lead from the sample.

The working detection limit of ASV for blood is comparable to that of the AAS flameless methods, while the relative precision is best with prior sample degradation, approximately 5 percent. The precision is less when the blood samples are run directly with the ion exchange reagents (Morrell and Giridhar, 1976), particularly at the low end of "normal" blood lead values. While AAS methods require attention to various spectral interferences to achieve satisfactory performance, electrochemical methods such as ASV require consideration of such factors as the effects of co-reducible metals and agents that complex lead and alter its reduction-oxidation (redox) potential properties. Chelants used in therapy, particularly penicillamine, may interfere, as does blood copper, which may be elevated in pregnancy and during such disease states as leukemia, lymphoma, and hyperthyroidism (Berman, 1981).

Correction of whole blood lead values for hematocrit, although carried out in the past, is probably not appropriate and not commonly done at present. While the erythrocyte is the carrier for virtually all lead in blood, the saturation capacity of the red blood cell (RBC) for lead is so high that it can still carry lead even at highly toxic levels (Kochen and Greener, 1973). Kochen and Greener (1973) also showed that acute or chronic dosing at a given lead level in rats with a wide range of hematocrits (induced by bleeding) gave similar blood lead values. Rosen et al. (1974), based on studies of hematocrit, plasma, and whole blood lead in children, noted hematocrit correction was not necessary, a view supported by Chisolm (1974).

9.2.2.2 Lead in Plasma. While virtually all of the lead present in whole blood is bound to the erythrocyte (Robinson et al., 1958; Kochen and Greener, 1973), lead in plasma is transported to affected tissues. Therefore, every precaution must be taken to use nonhemolyzed blood samples for plasma isolation. The very low levels of lead in plasma require that more attention be paid to "ultra-clean" methods.

Rosen et al. (1974) used flameless AAS and microliter samples of plasma to measure plasma lead, with background correction for the smoke signal generated for the unmodified sample. Cavalleri et al. (1978) used a combination of solvent extraction of modified plasma with preconcentrating and flameless AAS. These authors noted that the method used by Rosen et al. (1974) permitted less precision and accuracy than did their technique, because a significantly smaller amount of lead was delivered to the furnace accessory.

DeSilva (1981), using a technique similar to that of Cavalleri et al. (1978), but collecting samples in heparinized tubes, claimed that the use of ethylenediaminetetraacetic acid (EDTA) as anticoagulant disturbs the cell-plasma distribution of lead enough to yield erroneous data. Much more care was given in this procedure to background contamination. In both cases, increasing levels of plasma lead were measured with increasing whole blood lead, suggesting an equilibrium ratio that contradicts the data of Rosen et al. (1974). They found a fixed level of 2-3 μg/dl plasma over a wide range of blood lead values. However, the actual levels of lead in plasma in the DeSilva (1981) study were much lower than those reported by Cavalleri et al. (1978).

Using IDMS and sample collection/manipulation in an "ultra-clean" facility, Everson and Patterson (1980) measured the plasma lead levels in two subjects, a control and a lead-exposed worker. The control had a plasma lead level of 0.002 μg/dl, several orders of magnitude lower than that seen with studies using less precise analytical approaches. The lead-exposed worker had a plasma level of 0.2 μg/dl. Several other reports in the literature using IDMS noted somewhat higher values of plasma lead (Manton and Cook, 1979; Rabinowitz et al., 1974), which Everson and Patterson (1980) have ascribed to problems of laboratory contamination.

Using tracer lead to minimize the impact of contamination results in a value of 0.15 µg/dl (Rabinowitz et al., 1974).

With appropriate plasma lead methodology, reported lead levels are extremely low, the degree varying with the methods used to measure such concentrations. While the data of Everson and Patterson (1980) were obtained from only two subjects, it seems unlikely that using more subjects would result in a plasma lead range extending upward to the levels seen with ordinary methodology in ordinary laboratory surroundings. The above considerations are important when discussing appropriate methodology for plasma analysis, and the Everson and Patterson (1980) report indicates that some doubt surrounds results obtained with conventional methods. Although not the primary focus of their study, the values obtained by Everson and Patterson (1980) for whole blood lead, unlike the data for plasma, are within the ranges for unexposed (11 µg/dl) and exposed (80 µg/dl) subjects generally reported with other methods. This agreement would suggest that, for the most part, reported values do actually reflect *in vivo* blood lead levels rather than sampling problems or inaccurate methods.

9.2.2.3 *Lead in Teeth*. When analyzing shed deciduous or extracted permanent teeth, some investigators have used the whole tooth after surface cleaning to remove contaminating lead (e.g., Moore et al., 1978; Fosse and Justesen, 1978; Mackie et al., 1977), while others have measured lead in dentine (e.g., Shapiro et al., 1973; Needleman et al., 1979; Al-Naimi et al., 1980). Several reports (Grandjean et al., 1979; Shapiro et al., 1973) have also described the analysis of circumpulpal dentine, that portion of the tooth found to have the highest relative fraction of lead. Needleman et al. (1979) separated dentine by embedding the tooth in wax, followed by thin central sagittal sectioning. The dentine was then isolated from the sawed sections by careful chiseling.

Determining mineral and organic composition of teeth and their components requires the use of thorough chemical decomposition techniques, including wet ashing and dry ashing steps and sample pulverizing or grinding. In the procedure of Steenhout and Pourtois (1981), teeth are dry ashed at 450°C, powdered, and dry ashed again. The powder is then dissolved in nitric acid. Fosse and Justesen (1978) reduced tooth samples to a coarse powder by crushing in a vise, followed by acid dissolution. Oehme and Lund (1978) crushed samples to a fine powder in an agate mortar and dissolved the samples in nitric acid. Mackie et al. (1977) and Moore et al. (1978) dissolved samples directly in concentrated acids. Chatman and Wilson (1975) and Needleman et al. (1974) carried out wet ashing with nitric acid followed by dry ashing at 450°C. Oehme and Lund (1978) found that acid wet ashing of tooth samples yielded better results if carried out in a heated Teflon bomb at 200°C.

With regard to methods of measuring lead in teeth, AAS and ASV have been employed most often. With the AAS methods, the high mineral content of teeth tends to argue for isolating lead from this matrix before analysis. In the methods of Needleman et al. (1974) and Chatman and Wilson (1975), ashed residues in nitric acid were treated with ammonium nitrate and ammonium hydroxide to a pH of 2.8, followed by dilution and extraction with a methylisobutylketone solution of ammonium pyrrolidinecarbodithioate. Analysis was by flame AAS, using the 217.0-nm lead-absorption line. A similar procedure was employed by Fosse and Justesen (1978).

ASV has been successfully used in tooth lead measurement (Shapiro et al., 1973; Needleman et al., 1979; Oehme and Lund, 1978). As typified by the method of Shapiro et al. (1973), samples of dentine were dissolved in a small volume of low-lead concentrated perchloric acid and diluted (5.0 ml) with lead-free sodium acetate solution. With deoxygenation, samples were analyzed in a commercial ASV unit, using a plating time of 10 min at a plating potential of -1.05 V. Anodic sweeping was at a rate of 60 mV/sec with a variable current of 100-500 μA. Since lead content of teeth is higher than in most samples of biological media, the relative precision of analysis with appropriate accommodation of the matrix effect, such as the use of matrix-matched standards, in the better studies indicates a value of approximately 5-7 percent.

In an analysis of lead levels in permanent teeth of Swedish subjects, Moller et al. (1982) used particle-induced X-ray emission (PIXE). While this method permits analysis with minimal contamination risk, it measures only coronal dentine, which is relatively less revealing about cumulative exposure than secondary or circumpulpal dentine.

All of the above methods involve shed or extracted teeth and consequently provide a retrospective determination of lead exposure. In Bloch et al.'s (1976) procedure, tooth lead is measured in situ using an X-ray fluorescence technique. A collimated beam of radiation from ^{57}Co was allowed to irradiate the upper central incisor teeth of the subject. Using a relatively safe 100-sec irradiation time and measurement of $K_{\alpha 1}$ and $K_{\alpha 2}$ lead lines via a germanium diode and a pulse-height analyzer for signal processing, lead levels of 15 ppm or higher could be measured. Multiple measurement by this method would be very useful in prospective studies because it would show the "ongoing" rate of increase in body lead burden. Furthermore, when combined with serial blood sampling, it would provide data for blood lead-tooth lead relationships.

9.2.2.4 Lead in Hair. Hair constitutes a noninvasive sampling source with virtually no problems with sample stability on extended storage. However, the advantages of accessibility and stability are offset by the problem of assessing external contamination of the hair surface by atmospheric fallout, hand dirt, lead in hair preparations, etc. Thus, such samples are probably of less value overall than those from other media.

The various methods that have been employed for removal of external lead have been reviewed (Chatt et al., 1980; Gibson, 1980; Chattopadhyay et al., 1977). Cleaning techniques obviously should be vigorous enough to remove surface lead but not so vigorous as to remove the endogenous fraction. To date, no published cleaning procedure has been proven reliable enough to permit acceptance of reported levels of lead in hair. Such a demonstration would have to use lead isotopic studies with both surface and endogenous isotopic lead removal monitored as a function of a particular cleaning technique.

9.2.2.5 Lead in Urine. Analysis of lead in urine is complicated by its relatively low concentrations (lower than in blood in many cases) as well as by the complex mixture of mineral elements present. Lead levels are higher, of course, in cases where lead mobilization or therapy with chelants is in progress, but in these cases samples must be analyzed to account for lead bound to chelants such as EDTA. Such analysis requires either sample ashing or the use of standards containing the chelant. Although analytical methods have been published for the direct analysis of lead in urine, samples are probably best wet ashed before analysis, using the usual mixtures of nitric plus sulfuric and/or perchloric acids.

Both AAS and ASV methods have been applied to urine lead analyses, the former employing either direct analysis of ashed residues or a preliminary chelation-extraction step. With flame AAS, ashed urine samples must invariably be extracted with a chelant such as ammonium pyrrolidinecarbodithioate in methylisobutylketone to achieve reasonably satisfactory results. Furthermore, direct analysis creates mechanical problems with burner operation, due to the high mineral content of urine, and results in considerable maintenance problems with equipment. The procedure of Lauwerys et al. (1975) is typical of flame AAS methods with preliminary lead separation. Because of the relatively greater sensitivity of graphite furnace (flameless) AAS, this variation of the method has been applied to urine analysis. In scattered reports of such analyses, adequate performance for direct sample analysis seems to require steps to minimize matrix interference. A typical example of one of the better direct analysis methods is that of Hodges and Skelding (1981). Urine samples were mixed with iodine solution and heated, then diluted with a special reagent containing ammonium molybdate, phosphoric acid, and ascorbic acid. Small aliquots (5 µl) were delivered to the furnace accessory of an AAS unit containing a graphite tube pretreated with ammonium molybdate. The relative standard deviation of the method is reported to be about 6 percent. In the method of Legotte et al. (1980), such tube treatment and sample modifications were not employed and the average precision figure was 13 percent.

Compared with various AAS methods, ASV has been less frequently employed for urine lead analysis. From a survey of available electrochemical methods in general, such techniques applied to urine appear to require further development. Franke and de Zeeuw (1977) used differential-pulse ASV as a screening tool for lead and other elements in urine. Jagner et al. (1979) described analysis of urine lead using potentiometric stripping. In their procedure the element was preconcentrated at a thin-film mercury electrode as in conventional ASV, but deoxygenated samples were reoxidized with either oxygen or mercuric ions after the circuit was disconnected.

As noted in Section 9.1.1.2, if collection of 24-hr samples is not possible, spot sampling of lead in urine can be conducted, and results should be expressed per unit creatinine.

9.2.2.6 Lead in Other Tissues. Bone samples of experimental animal or human autopsy origin require preliminary cleaning procedures for removal of muscle and connective tissue, with care being taken to minimize sample contamination. As is the case with teeth, samples must be chemically decomposed before analysis. Satisfactory instrumental methods for bone lead analysis comprise a much smaller literature than is the case for other media.

Wittmers et al. (1981) have described the measurement of lead in dry ashed (450°C) bone samples using flameless AAS. Ashed samples were weighed and dissolved in dilute nitric acid containing lanthanum ion, the latter being used to suppress interference from bone elements. Small volumes (20 µl) and high calcium content required that atomization be done at 2400°C to avoid condensation of calcium within the furnace. Quantification was by the method of additions. Relative precision was 6-8 percent at relatively high lead content (60 µg/g ash) and 10-12 percent at levels of 14 µg/g ash or less.

Ahlgren et al. (1980) described the application of X-ray fluorescence analysis to in vivo lead measurement in the human skeleton, using tibia and phalanges. In this technique, irradiation is carried out with a dual ^{57}Co gamma ray source. The generated $K_{\alpha 1}$ and $K_{\alpha 2}$ lead lines are detected with a lithium-drifted germanium detector. The detection limit is 20 ppm.

Soft organs differ from other biological media in the extent of anatomic heterogeneity as well as lead distribution, e.g., brain versus kidney. Hence, sample analysis involves either discrete regional sampling or the homogenizing of an organ. The efficiency of the latter can vary considerably, depending on the density of the homogenate, the efficiency of rupture of the formed elements, and other factors. Glass-on-glass homogenizing should be avoided because lead is liberated from the glass matrix with abrasion.

AAS, in its flame or flameless variations, is the method of choice in many studies. In the procedure of Slavin et al. (1975), tissues were wet ashed and the residues taken up in dilute acid and analyzed with the furnace accessory of an AAS unit. A large number of reports representing slight variations of this basic technique have appeared over the years (Lawrence, 1982, 1983). Flame procedures, being less sensitive than the graphite furnace method, require more sample than may be available or are restricted to measurement in tissues where levels are relatively high, e.g., kidney. In the method of Farris et al. (1978), samples of brain, liver, lung, or spleen (as discrete segments) were lyophilized and then solubilized at room temperature with nitric acid. Following neutralization, lead was extracted into methylisobutylketone with ammonium pyrrolidinecarbodithioate and aspirated into the flame of an AAS unit. The reported relative precision was 8 percent.

9.2.3 Quality Assurance Procedures In Lead Analysis

Regardless of technical differences among the different methodologies for lead analysis, one can define the quality of such techniques as being of certain categories: (1) poor accuracy and poor precision; (2) poor accuracy and good precision; or (3) good accuracy and good precision. In terms of available information, the major focus in assessing quality has been on blood lead determinations.

According to Boutwell (1976), the use of quality control testing for lead measurement rests on four assumptions: (1) that the validity of the specific procedure for lead in some matrix has been established; (2) that the stability of the factors making up the method has been both established and manageable; (3) that the validity of the calibration process and the calibrators with respect to the media being analyzed has been established; and (4) that surrogate quality control materials of reliably determined analyte content can be provided. These assumptions, when translated into practice, revolve around steps employed within the laboratory, using a battery of "internal checks" and a further reliance on "external checks" such as a formal, well-organized, multi-laboratory proficiency testing program.

Analytical quality protocols can be further divided into start-up and routine procedures, the former entailing the establishment of detection limits, "within-run" and "between-run" precision, and recovery of analyte. When a new method is adopted for some specific analytical advantage, the procedure is usually tested inside or outside the laboratory for comparative performance. For example, Hicks et al. (1973) and Kubasik et al. (1972) reported that flameless techniques for measuring lead in whole blood had a satisfactory correlation with results using conventional flame procedures. Matson et al. (1971) noted a good agreement between ASV and both AAS and dithizone colorimetric techniques. The problem with such comparisons is that the reference method is assumed to be accurate for the particular level of lead in a given matrix. High correlations obtained in this manner may simply indicate that two inaccurate methods are simultaneously performing with the same level of precision.

Preferable approaches for assessing accuracy are the use of certified samples determined by a definitive method or direct comparison of different techniques with a definitive procedure. For example, Eller and Hartz (1977) compared the precision and accuracy of five available methods for measuring lead in blood: dithizone spectrometry, extraction and tantalum boat AAS, extraction and flame aspiration AAS, direct aspiration AAS, and graphite furnace AAS techniques. Porcine whole blood certified by NBS using IDMS at 1.00 μg/g (±0.023) was tested and all methods were found to be equally accurate. The tantalum boat technique was the least precise. The obvious limitation of data from this technique is that they relate to a high blood lead content, suitable for use in measuring the exposure of lead workers or in some other occupational context, but less appropriate for clinical or epidemiological investigations.

Boone et al. (1979) compared the analytical performance of 113 laboratories using various methods and 12 whole blood samples (blood from cows fed a lead salt) certified as to lead content using IDMS at the NBS. Lead content ranged from 13 to 102 µg/dl, determined by ASV and five variations of AAS. The order of agreement with NBS values, i.e., relative accuracy, was as follows: extraction > ASV > tantalum strip > graphite furnace > Delves cup > carbon rod. The AAS methods all showed bias, having positive values at less than 40 µg/dl and negative values at levels greater than 50 µg/dl. ASV showed less of a positive bias problem, although it was not bias free within either of the blood lead ranges. In terms of relative precision, the ranking was: ASV > Delves cup > tantalum strip > graphite furnace > extraction > carbon rod. The overall ranking in accuracy and precision indicated: ASV > Delves cup > extraction > tantalum strip > graphite furnace > carbon rod. As the authors cautioned, the above data should not be taken to indicate that any established laboratory using one particular technique would not perform better; rather, it should be used as a guide for newer facilities choosing among methods.

A number of steps in quality assurance pertinent to the routine measurement of lead are necessary in an ongoing program. With respect to internal checks of routine performance, these steps include calibration and precision and accuracy testing. With biological matrices, the use of matrix-matched standards is quite important, as is an understanding of the range of linearity and variation of calibration curve slopes from day to day. Analyzing a given sample in duplicate is common practice, with further replication carried out if the first two determinations vary beyond a predetermined range. A second desirable step is the analysis of samples collected in duplicate but analyzed "blind" to avoid bias.

Monitoring accuracy within the laboratory is limited to the availability of control samples having a certified lead content in the same medium as the samples being analyzed. Controls should be as physically close to the media being analyzed as possible. Standard reference materials (SRMs), such as orchard leaves and lyophilized bovine liver, are of help in some cases, but NBS-certified blood samples are needed for the general laboratory community. Whole blood samples, prepared and certified by the marketing facility (TOX-EL, A.R. Smith Co., Los Angeles, CA; Kaulson Laboratories, Caldwell, NJ; Behringwerke AG, Marburg, W. Germany; and Health Research Institute, Albany, NY) are available commercially. With these samples, attention must be paid to the reliability of the methods used by reference laboratories. The use of such materials, from whatever source, must minimize bias; for example, the attention given control specimens should be the same as that given routine samples.

Finally, the most important form of quality assurance is the ongoing assessment of laboratory performance by proficiency testing programs using externally provided specimens for analysis. Earlier interlaboratory surveys of lead measurement in blood and in urine indicated that a number of laboratories had performed unsatisfactorily, even when dealing with high concentrations of lead (Keppler et al., 1970; Donovan et al., 1971; Berlin et al., 1973), although some of the problems may have originated in the preparation and status of the blood samples during and after distribution (World Health Organization, 1977). These earlier tests for proficiency indicated the following: (1) many laboratories were able to achieve a good degree of precision within their own facilities; (2) the greater the number of samples routinely analyzed by a facility, the better the performance; and (3) 30 percent of the laboratories routinely analyzing blood lead reported values differing by more than 15 percent from the true level (Pierce et al., 1976).

In the more recent, but very limited, study of Paulev et al. (1978), five facilities participated in a survey, using samples to which known amounts of lead had been added. For lead in both whole blood and urine, the interlaboratory coefficient of variation was reported to be satisfactory, ranging from 12.3 to 17.2 percent. Aside from its limited scope, this study used "spiked" instead of in vivo lead, so that extraction techniques used in most of the laboratories surveyed would have given misleadingly better results in terms of actual recovery.

Maher et al. (1979) described the outcome of a proficiency study involving up to 38 laboratories that analyzed whole blood pooled from a large number of samples submitted for blood lead testing. The Delves cup technique was the most heavily represented, followed by the chelation-extraction plus flame AAS method and the graphite furnace AAS method. ASV was used by only approximately 10 percent of the laboratories, so that the results basically portray AAS methods. All laboratories had about the same degree of accuracy, with no evidence of consistent bias, while the interlaboratory coefficient of variation was approximately 15 percent. A subset of this group, certified by the American Industrial Hygiene Association (AIHA) for air lead, showed a corresponding precision figure of approximately 7 percent. Over time, the subset of AIHA-certified laboratories remained about the same in proficiency, while the other facilities showed continued improvement in both accuracy and precision. This study indicates that program participation does help the performance of a laboratory doing blood lead determinations.

The most comprehensive proficiency testing program is that carried out by the Centers for Disease Control (CDC) of the U.S. Public Health Service (USPHS). This testing program consists of two operationally and administratively distinct subprograms, one conducted by the Center for Environmental Health (CEH) and the other by the Licensure and Proficiency Testing Division, Laboratory Improvement Program Office (LIPO). The CEH program is directed at facilities involved in lead poisoning prevention and screening, while LIPO is concerned with laboratories seeking certification under the Clinical Laboratories Improvement Act of 1967 as well as under regulations of the Occupational Safety and Health Administration (OSHA). Both the CEH and LIPO protocols involve the use of bovine whole blood certified as to content by reference laboratories (6 in the CEH program, 20-23 in LIPO) with an ad hoc target range of ±6 µg/dl for values of 40 µg/dl or less and ±15 percent for higher levels. Three samples are provided monthly from CEH, for a total of 36 yearly, while LIPO participants receive three samples quarterly (12 samples yearly). Use of a fixed range rather than a standard deviation has the advantage of allowing the monitoring of overall laboratory improvement.

For fiscal year (FY) 1981, 114 facilities were in the CEH program, 92 of them participating for the entire year. Of these, 57 percent each month reported all three samples within the target range, and 85 percent on average reported two out of three samples correctly. Of the facilities reporting throughout the year, 95 percent had a 50 percent or better performance, i.e., 18 blood samples or better. Comparing the summary data for FY 1981 with earlier annual reports, one sees considerable improvement in the number of laboratories achieving higher levels of proficiency. For the interval FY 1977-79, there was a 20 percent increase in the number correctly analyzing more than 80 percent of all samples and a 33 percent decrease in those reporting less than 50 percent correct. In the last several years, FY 1979-81, overall performance has more or less stabilized.

With the LIPO program for 1981 (Dudley, 1982), the overall laboratory performance averaged across all quarters was 65 percent of the laboratories analyzing all samples correctly and approximately 80 percent performing well with two of three samples. Over the 4 years of this program, an increasing ability to analyze lead in blood correctly has been demonstrated. Dudley's (1982) survey also indicates that reference laboratories in the LIPO program are becoming more accurate relative to IDMS values, i.e., bias over the blood lead range is contracting.

Current OSHA criteria for certification of laboratories measuring occupational blood lead levels require that eight of nine samples, 89 percent, be within 6 µg/dl or 15 percent of reference laboratory means for samples sent over the three previous quarters (U.S. Occupational Safety and Health Administration, 1982). These criteria reflect the ability of a number of laboratories to perform at this level.

Note that most proficiency programs, including the CEH and LIPO surveys, are appropriately concerned with blood lead levels encountered in such cases as pediatric screening for excessive exposure to lead or in occupational exposures. As a consequence, underrepresentation of lead values in the low end of the "normal" range occurs. In the CEH distribution for FY 1981, four samples (11 percent) were below 25 µg/dl. The relative performance of the 114 facilities with these samples indicates outcomes much better than with the whole sample range. This relative distribution of low blood lead samples appears to have continued to the present.

The National Bureau of Standards has recently made available certified porcine blood lead standard reference material (SRM 955) at two levels of blood lead. Certified urine lead samples are also being offered.

9.3 DETERMINATION OF ERYTHROCYTE PORPHYRIN (FREE ERYTHROCYTE PROTOPORPHYRIN, ZINC PROTOPORPHYRIN)

9.3.1 Methods of Erythrocyte Porphyrin Analysis

Lead exposure results in inhibition of the final step in heme biosynthesis, the insertion of iron into protoporphyrin IX to form heme. Inhibition of this step leads to an accumulation of the porphyrin, with zinc (II) occupying the position normally filled by iron. Depending on the particular method of analysis, zinc protoporphyrin (ZPP) itself or the metal-free form, free erythrocyte protoporphyrin (FEP), is measured. FEP generated as a consequence of chemical manipulation should be kept distinct from the metal-free form biochemically produced in the disease, erythropoietic protoporphyria. The chemical or "wet" methods measure FEP or ZPP, depending upon the relative acidity of the extraction medium. The hematofluorometer in its commercially available form measures ZPP.

Porphyrins are labile due to photochemical decomposition; hence, samples must be protected from light during collection and handling and analyzed as soon as possible. Hematocrits must also be obtained to adjust for anemic subjects.

In terms of methodological approaches for erythrocyte porphyrin (EP) analysis, virtually all methods now in use exploit the ability of porphyrins to undergo intense fluorescence when excited at the appropriate wavelength of light. Such fluorometric techniques can be further classified as wet chemical micromethods or as micromethods using a recently developed instrument, the hematofluorometer. The latter involves direct measurement in whole blood. Because the mammalian erythrocyte contains all of the EP in whole blood, either packed cells or whole blood may be used, although the latter is more expedient.

Because of the relatively high sensitivity of fluorometric measurement for FEP or ZPP, laboratory methods for spectrofluorometric analysis require a relatively small sample of blood; hence, microtechniques are currently the most popular in most laboratories. These involve either liquid samples or blood collected on filter paper, the latter used particularly in field sampling.

As noted above, chemical methods for EP analysis measure either FEP, where zinc is chemically removed, or ZPP, where zinc is retained. The procedures of Piomelli and Davidow (1972), Granick et al., (1972), and Chisholm and Brown (1975) typify "free" EP methods, while those of Lamola et al. (1975), Joselow and Flores (1977), and Chisolm and Brown (1979) involve measurement of zinc EP.

In Piomelli and Davidow's (1972) microprocedure, small volumes of whole blood, analyzed either directly or after collection on filter paper, were treated with a suspension of Celite in saline followed by a 4:1 mixture of ethyl acetate to glacial acetic acid. After agitation and centrifugation, the supernatant was extracted with 1.5N HCl. The acid layer was analyzed fluorometrically using an excitation wavelength of 405 nm and measurement at 615 nm. Blood collected on filter paper discs was first eluted with 0.2 ml H_2O. The filter paper method was found to work just as well as liquid samples of whole blood. Protoporphyrin IX was employed as a quantitative standard. Granick et al. (1972) used a similar microprocedure, but it differed in the concentration of acid employed and the use of a ratio of maxima.

In Chisolm and Brown's (1975) variation, volumes of 20 µl of whole blood were treated with ethyl acetate/acetic acid (3:1) and briefly mixed. The acid-extraction step was done with 3N HCl, followed by a further dilution step with more acid if the value was beyond the range of the calibration curve. In this procedure, protoporphyrin IX was used as the working standard, with coproporphyrin (a precursor to protoporphyrin) used to monitor the calibration of the fluorometer and any variance with the protoporphyrin standard.

Lamola et al. (1975) analyzed the ZPP as such in their procedure. Small volumes of blood (20 µl) were worked up in a detergent (dimethyl dodecylamine oxide) and phosphate buffer solution, and fluorescence was measured at 594 nm with excitation at 424 nm. In the variation of Joselow and Flores (1977), 10 µl of whole blood was diluted 1000-fold, along with protoporphyrin (Zn) standards, with the detergent-buffer solution. Note that the ZPP standard is virtually impossible to obtain in pure form. Chisolm and Brown (1979) reported the use of protoporphyrin IX plus very pure zinc salt for such standards.

In the single-extraction variation of Orfanos et al. (1977), liquid samples of whole blood (40 µl) or blood on filter paper were treated with acidified ethanol. The mixtures were agitated and centrifuged, and the supernatants analyzed directly in fluorometer cuvettes. For blood samples on filter paper, blood was first leached from the paper with saline by soaking for 60 min. Coproporphyrin was used as the quantitative standard. The correlation coefficient with the Piomelli and Davidow (1972) procedure (see above) over the range 40-650 µg EP/dl RBCs was $r = 0.98$. As in the above methods, ZPP itself is measured.

Regardless of the extraction methods used, some instrumental parameters are important, including the variation between cut-offs in secondary emission filters and variation among photomultiplier tubes in the red region of the spectrum. Hanna et al. (1976) compared four micromethods for EP analysis: double extraction with ethyl acetate/acetic acid and with HCl (Piomelli and Davidow, 1972), single extraction with either ethanol or acetone (Chisolm et al., 1974), and direct solubilization with detergent (Lamola et al., 1975). Of these, the ethyl acetate and ethanol procedures were satisfactory; complete extraction occurred only with the ethyl acetate/acetic acid method. In the method of Chisholm et al. (1974), the choice of acid and its concentration appears to be more significant than the choice of organic solvent.

The levels of precision with these wet micromethods differ with the specifics of analysis. Piomelli (1973) reported a coefficient of variation (C.V.) of 5 percent, compared to Herber's (1980) observation of 2-4 percent for the methods per se and 6-11 percent total C.V., which included precision of samples, standards, and day-to-day variation. The Lamola et al. (1975) method for ZPP measurement was found to have a C.V. of 10 percent (same day, presumably), whereas Herber (1980) reported a day-to-day C.V. of 9.3-44.6 percent. Herber (1980) also found that the wet chemical micromethod of Piomelli (1973) had a detection limit of 20 μg EP/dl whole blood, while that of Lamola et al. (1975) was sensitive to 50 μg EP/dl whole blood.

The recent development of direct instrumental measurement of ZPP with the hematofluorometer has made it possible to use EP measurement in field screening for lead exposure in large groups of subjects. However, hematofluorometers were developed for and remain most useful for lead screening programs; they were not meant to be laboratory substitutes for the chemical methods of EP analysis. (See Section 9.3.2 for a comparative discussion.) As originally developed by Bell Laboratories (Blumberg et al., 1977) and now produced commercially, the apparatus employs front-face optics, in which excitation of the fluorophore is at an acute angle to the sample surface, with emitted light emerging from the same surface and thus being detected. Routine calibration requires a stable fluorescing material with spectra comparable to ZPP; the triphenylmethane dye Rhodamine B is used for this purpose. Absolute calibration requires adjusting the microprocessor-controlled readout system to read the known concentration of ZPP in reference blood samples, the latter calibration performed as frequently as possible.

Hematofluorometers are designed for measuring EP in samples containing oxyhemoglobin, i.e., capillary blood. Venous blood, therefore, must first be oxygenated, usually by moderate shaking for approximately 10 min (Blumberg et al., 1977; Grandjean and Lintrup, 1978). A second problem with hematofluorometer use, in contrast to wet chemical methods, is interference by bilirubin (Karačić et al., 1980; Grandjean and Lintrup, 1978). This interference occurs with relatively low levels of EP. At levels normally encountered in lead workers or subjects with anemia or nonoccupational lead exposure, the degree of such interference is not considered significant (Grandjean and Lintrup, 1978). Karačić et al. (1980) have found that carboxyhemoglobin (COHb) may pose a potential problem, but its relevance to EP levels of subjects exposed to lead has not been fully elucidated. Background fluorescence in cover glass may be a problem and should be tested in advance. Finally, the accuracy of the hematofluorometer appears to be affected by hemolyzed blood.

Competently employed, the hematofluorometer appears to be reasonably precise, but its accuracy may still be biased (see below). Blumberg et al. (1977) reported a C.V. of 3 percent over the entire range of ZPP values measured when using a prototype apparatus. Karacić et al. (1980) found the relative standard deviation to vary from 1 percent (0.92 mM ZPP/M Hb) to 5 percent (0.41 mM ZPP/M Hb) depending on concentration. Grandjean and Lintrup (1978) obtained a day-to-day C.V. of 5 percent using blood samples refrigerated for up to 9 weeks. Herber (1980) obtained a total C.V. of 4.1-11.5 percent.

A number of investigators have compared EP measured by the hematofluorometer with EP measured by the laboratory or wet chemical techniques, ranging from a single, intralaboratory comparison to interlaboratory performance testing. The latter included the EP proficiency testing program of the USPHS' CDC. Working with prototype instrumentation, Blumberg et al. (1977) obtained correlation coefficients of $r = 0.98$ (range: 50-800 μg EP/dl RBCs) and 0.99 (range: up to 1000 μg EP/dl RBCs) for comparisons with the Granick and Piomelli methods, respectively. Grandjean and Lintrup (1978), Castoldi et al. (1979) and Karacić et al. (1980) have achieved equally good correlation results.

Several reports (Culbreth et al., 1979; Scoble et al., 1981; Smith et al., 1980) have described the application of high-performance liquid chromatography (HPLC) to the analysis of either FEP or ZPP in whole blood. In one of the studies (Scoble et al., 1981), the protoporphyrins as well as coproporphyrin and mesoporphyrin IX were reported to be determined on-line fluorometrically in less than 6 min using 0.1 ml of blood sample. The HPLC approach remains to be tested in interlaboratory proficiency programs.

9.3.2 Interlaboratory Testing of Accuracy and Precision in EP Measurement

In a relatively early attempt to assess interlaboratory proficiency in EP measurement, Jackson (1978) reported results of a survey of 65 facilities that analyzed 10 whole blood samples by direct measurement with the hematofluorometer or by one of the wet chemical methods. In this survey, the instrumental methods had a low bias compared to the extraction techniques but tended to show better interlaboratory correlation.

At present, CDC's ongoing EP proficiency testing program constitutes the most comprehensive assessment of laboratory performance (U.S. Centers for Disease Control, 1981). Every month, three samples of whole blood prepared at the University of Wisconsin Laboratory of Hygiene are forwarded to participants. Reference means are determined by a group of reference laboratories with a target range of ±15 percent across the whole range of EP values. For FY 1981, of the 198 laboratories participating, 139 facilities were involved for the entire year. Three of the 36 samples in the year were not included. Of the 139 year-long participants, 93.5 percent had better than half of the samples within the target range, 84.2 percent performed satisfactorily with 70 percent or more of the samples within range, and 50.4 percent of all laboratories had 90 percent or more of the samples yielding the correct results. The participants as a whole showed greater proficiency than in the previous year. Of the various methods currently used, the hematofluorometer direct measurement technique was most heavily represented. For example, in the January 1982 survey of the three major techniques, 154 participants used the hematofluorometer, 30 used the Piomelli method, and 7 used the Chisolm/ Brown method.

A recent survey by Balamut et al. (1982) raises the troublesome observation that the use of commercially available hematofluorometers may yield satisfactory proficiency results but still be inaccurate when compared to the wet chemical method using freshly drawn whole blood. Two hematofluorometers in wide use performed well in proficiency testing but showed an approximately 30 percent negative bias with clinical samples analyzed by both instrument and chemical microtechniques. This bias leads to false negatives when used in screening. Periodic testing of split samples by both fluorometer and chemical means is necessary to monitor, and correct for, instrument negative bias. The basis of the bias is much more than can be explained by the difference between FEP and ZPP. This survey points out precautions noted earlier on the restrictive use of the hematofluorometer to screening situations.

Mitchell and Doran (1985) compared EP values measured in their laboratory by the chemical extraction technique with results obtained by the hematofluorometer in 21 other laboratories. These workers found that (a) hematofluorometer results were 11-28 percent lower than the corresponding chemical method values, (b) hematofluorometers demonstrated mean error of up to 3 percent for proficiency samples, and (c) hematofluorometers showed a negative bias of 20 percent at EP levels of 50 μg/dl and would miss about one third (false negatives) of children at or somewhat above this level.

One factor that can be important in the relative accuracy of the hematofluorometer versus wet chemical methods is the relative stability of ZPP levels as a proportion of total EP across that age range in childhood of most interest in screening. Hammond and coworkers (1984) have observed that the fraction of ZPP versus total EP was at a relative minimum at 3 months of age in 165 children serially tested, and that it increased to 1.0 by around 33 months of age. These observations suggest that this variation of proportionality with age should be taken into account when screening children under approximately 30 months of age and when the hematofluorometer is the chief means of EP quantification.

The technical basis for this age-related change in proportionality may be spectroscopic, i.e., changes in erythrocyte size over this age range would lead to differences in cell packing, which in turn would affect fluorescence yield during front-face irradiation in the hematofluorometer. A second factor noted by the authors may have to do with relative availability of zinc. Since zinc deficiency is common at this stage of development (see Chapter 10), bioavailability of zinc for a nonessential complexing with FEP would be restricted by homeostatic sparing of the element for physiological needs. However, since the work of

Chisolm and Brown (1979), using a chemical method, did not reveal any disparity between the two forms in subjects of the same age range, there is probably an instrumental artifact operating here.

9.4 MEASUREMENT OF URINARY COPROPORPHYRIN

The elevation of urinary coproporphyrin (CP-U) with lead intoxication served as a useful indicator of such intoxication in children and lead workers for many years. Although analysis of CP-U has declined considerably in recent times with the development of other testing methods, such as measurement of EP, it still has the advantage of showing active intoxication (Piomelli and Graziano, 1980).

The standard method of CP-U determination is the fluorometric procedure described by Schwartz et al. (1951). Urine samples are treated with acetate buffer and aqueous iodine, the latter converting coproporphyrinogen to coproporphyrin (CP). The porphyrin is partitioned into ethyl acetate and back extracted (4 times) with 1.5N HCl. Coproporphyrin is employed as the quantitative standard. Working curves are linear below 5 μg CP/l urine.

In the absorption spectrometric technique of Haeger-Aronsen (1960), iodine is also used to convert coproporphyrinogen to CP. The extractant is ethyl ether, from which the CP is removed with 0.1N HCl. Absorption is read at three wavelengths, 380, 430, and the Soret maximum at 402 nm. Quantification is carried out using an equation involving the three wavelengths.

9.5 MEASUREMENT OF DELTA-AMINOLEVULINIC ACID DEHYDRASE ACTIVITY

Delta-aminolevulinic acid dehydrase (5-aminolevulinate hydrolase; porphobilinogen synthetase; E.C. 4.2.1.24; i.e., ALA-D) is an allosteric sulfhydryl enzyme that mediates the conversion of two units of δ-aminolevulinic acid (δ-ALA) to porphobilinogen, a precursor in the heme biosynthetic pathway to the porphyrins. Lead's inhibition of the activity of this enzyme is the enzymological basis of ALA-D's diagnostic utility in assessing lead exposure using erythrocytes.

A number of sampling precautions are necessary when measuring this enzyme's activity. ALA-D activity is modified by the presence of zinc as well as lead. Consequently, blood collection tubes that have high background zinc content, mainly in the rubber stoppers, must be avoided completely or care must be taken to avoid stopper contact with blood. Nackowski et al. (1977) observed that the presence of zinc in blood collection tubes is a pervasive problem, and plastic-cup tubes appear the only practical means to avoid it. To guard against zinc in the tube itself, one should determine the extent of zinc leachability by blood and use one tube lot, if possible. Heparin is the anticoagulant of choice, because the lead binding agent, EDTA, or other chelants would affect the lead-enzyme interaction. The relative instability of the enzyme in blood makes rapid determinations of activity necessary, preferably as soon after collection as possible. Even with refrigeration, analysis of activity should be done within 24 hr (Berlin and Schaller, 1974). Furthermore, porphobilinogen is light labile, which requires that the assay be done under restricted light.

Various procedures for ALA-D activity measurement are chemically based on measurement of porphobilinogen generated from the substrate. Delta-ALA porphobilinogen is condensed with p-dimethylaminobenzaldehyde (Ehrlich's reagent) to yield a chromophore measured at 553 nm in a spectrophotometer. In the European Standardized Method for ALA-D activity measurement (Berlin and Schaller, 1974), developed with the collaboration of nine laboratories for use with blood samples having relatively low lead content, triplicate blood samples (0.2 ml) are hemolyzed, along with a blood blank, with water for 10 min at 37°C. Samples are then mixed with δ-ALA solution and incubated for 60 min. The enzyme reaction is terminated by addition of a solution of mercury (II) in trichloroacetic acid, followed by centrifugation and filtration. Filtrates are mixed with modified Ehrlich's reagent (p-dimethylaminobenzalehyde in trichloroacetic/perchloric acid mixture) and allowed to react for 5 min, followed by chromophore measurement in a spectrophotometer at 555 nm. Activity is quantified in terms of μM δ-ALA/min·l erythrocytes. Note that the amount of phosphate for Solution A in Berlin & Schaller's (1974) report should be 1.78 g, not the 1.38 g stated. In a microscale variation, Granick et al. (1973) used only 5 μl of blood and terminated the assay by trichloroacetic acid.

In comparing various reports concerning the relationship between lead exposure and ALA-D inhibition, attention should be paid to the units of activity measurement employed with the different techniques. Berlin and Schaller's (1974) procedure expresses activity as μM δ-ALA/min·l cells, while Tomokuni's (1974) method expresses activity as μM porphobilinogen/hr/ml cells. Similarly, when comparing the Bonsignore et al. (1965) procedure to that of Berlin and Schaller (1974), a conversion factor of 3.8 is necessary when converting from Bonsignore to European Standard Method units (Trevisan et al., 1981).

Several factors have been shown to affect ALA-D activity. Rather than measuring enzyme activity in blood once, Granick et al. (1973) measured activity before and after treatment with dithiothreitol, an agent that reactivates the enzyme by complexing lead. The ratio of activated to unactivated enzymes versus blood lead levels accommodates inherent differences in enzyme activity among individuals due to genetic factors and other reasons. Other agents for such activation include zinc (Finelli et al., 1975) and zinc plus glutathione (Mitchell et al., 1977). In the Mitchell et al. (1977) study, nonphysiological levels of zinc were used. Wigfield and Farant (1979) found that enzyme activity is related to assay pH; thus, reduced activity from such a pH-activity relationship could be misinterpreted as lead inhibition. These researchers find that pH shifts away from optimal, in terms of activity, as blood lead content increases and the incubation step proceeds.

9.6 MEASUREMENT OF DELTA-AMINOLEVULINIC ACID IN URINE AND OTHER MEDIA

Delta-aminolevulinic acid (δ-ALA) levels increase with elevated lead exposure, because of the inhibitory effect of lead on the activity of ALA dehydrase and/or the increase of ALA synthetase activity by feedback derepression. The result is that this intermediate in heme biosynthesis rises in the body and eventually results in increased urinary excretion. The measurement of this metabolite in urine provides an indication of the level of lead exposure.

The ALA content of urine samples (ALA-U)is stable for approximately 2 weeks or more if urine samples are acidified with tartaric or acetic acid and kept refrigerated. Values of ALA-U are adjusted for urine density if concentration is expressed in mg/l or is measured per gram creatinine. As noted in the case of urinary lead measurement, 24-hr collection is more desirable than spot sampling.

Five manual procedures and one automated procedure for urinary ALA measurement are most widely used. Mauzerall and Granick (1956) and Davis and Andelman (1967) described the most involved procedures, requiring the initial chromatographic separation of ALA. The approach of Grabecki et al. (1967) omitted chromatographic isolation, whereas the automated variation of Lauwerys et al. (1972) omitted prechromatography but included the use of an internal standard. Tomokuni and Ogata (1972) omitted chromatography but employed solvent extraction to isolate the pyrrole intermediate.

Mauzerall and Granick (1956) condensed ALA with a β-dicarbonyl compound, acetylacetone, at pH 4.6 to yield a pyrrole intermediate (Knorr condensation reaction), which was further reacted with p-dimethylaminobenzaldehyde in perchloric/acetic acid. The samples were then read in a spectrophotometer at 553 nm 15 min after mixing. In this method, both porphobilinogen and ALA are separated from urine by means of a dual-column configuration of cation and anion exchange resins. The latter retains the porphobilinogen and the former separates ALA from urea. The detection limit is 3 μmol/l urine. In the modification of this method by Davis and Andelman (1967), disposable cation/anion resin cartridges were used, in a sequential configuration, to expedite chromatographic separation and increase the sample analysis rate. Commercial (Bio-Rad) disposable columns based on this design are now available and appear satisfactory.

In these two approaches (Mauzerall and Granick, 1956; Davis and Andelman, 1967), the problem of interference due to aminoacetone, a metabolite occurring in urine, is not taken into account. However, Marver et al. (1966) used Dowex-1 in a chromatographic step subsequent to the condensation reaction to form the pyrrole. This step separates the ALA derivative from that of the aminoacetone. Similarly, Schlenker et al. (1964) used a cation-exchange column to retain aminoacetone.

Tomokuni and Ogata (1972) condensed ALA with ethylacetoacetate and extracted the resulting pyrrole with ethyl acetate. The extract was then treated with Ehrlich's reagent and the resulting chromophore measured spectrophotometrically. Lauwerys et al. (1972) developed an automated ALA analysis method for lead worker screening in which ALA was added in known amount as an internal standard and the prechromatography was avoided. They reported a high correlation (r = 0.98, no range available) with the procedure of Mauzerall and Granick (1956).

Roels et al. (1974) compared the relative proficiency of four methods--those of Mauzerall and Granick (1956), Davis and Andelman (1967), the Lauwerys et al. (1972) automated version, and the Grabecki et al. (1967) method, which omits chromatographic separation and is normally used with occupational screening. The chromatographic methods gave identical results over the range of 0-60 mg ALA/l urine, while the automated method showed a positive bias at <6 mg/l. The Grabecki et al. (1967) technique was the least satisfactory of the procedures compared. Roels et al. (1974) also noted that commercial ion-exchange columns resulted in low variability (<10 percent).

Della Fiorentina et al. (1979) combined the Tomokuni and Ogata (1972) extraction method with a correction equation for urine density. Up to 25 mg ALA/l, the C.V. was ≤4 percent along with a good correlation (r = 0.937) with the Davis and Andelman (1967) technique. While avoiding prechromatography saves time, one must prepare a curve relating urine density to a correction factor for quantitative measurement.

Although ALA analysis is normally done with urine as the indicator medium, Haeger-Aronsen (1960) reported a similar colorimetric method for blood and MacGee et al. (1977) described a gas-liquid chromatographic (GLC) method for ALA in plasma as well as urine. Levels of ALA in plasma are much lower than those in urine. In the latter method, ALA was isolated from plasma, reacted with acetyl-acetone, and partitioned into a solvent (trimethylphenylhydroxide), which also served for pyrolytic methylation in the injection port of the gas-liquid chromatograph; the methylated pyrrole was more amenable to chromatographic isolation than the more polar precursor. For quantification, an internal standard, 6-amino-5-oxohexanoic acid, was used. The sample requirement is 3 ml plasma. Measured levels ranged from 6.3 to 73.5 ng ALA/ml plasma, and yielded values that were approximately tenfold lower than the colorimetric techniques (O'Flaherty et al., 1980).

In comparing the Haeger-Aronsen (1960) and MacGee et al. (1977) methods, a number of differences should be pointed out. First, the colorimetric approach of Haegar-Aronsen does not employ chromatographic steps to separate the ALA from other aminoketones, specifically aminoacetone and porphobilinogen. While these other aminoketones are not known to be positively correlated with blood lead, they would add a positive bias to the accuracy of the levels obtained. The GLC method of MacGee and coworkers does not measure simultaneously these aminoketones in either plasma or urine, and a reading of the published methodology and its application (O'Flaherty et al., 1980) indicates the procedure is acceptable for urinary ALA and levels of ALA in plasma associated with relatively high blood lead values, i.e., >40 µg/dl. The suitability of the GLC approach for relatively low levels of plasma ALA, i.e., at blood lead levels below 40 µg/dl, remains to be fully evaluated in the field. A careful reading of the MacGee et al. report suggests potential interferences with low levels of ALA measurement, while the methodology has not had wide use or multi-laboratory evaluation. Despite its added cost, a good overall method for assessing the relationship of plasma ALA to blood lead levels below 40 µg/dl, now an issue of controversy (see Chapter 12.3), would be use of the MacGee method in tandem with computerized multiple-ion monitoring in a mass spectrometer. This method is an absolute means of ALA identification as well as a sensitive means of quantification.

9.7 MEASUREMENT OF PYRIMIDINE-5'-NUCLEOTIDASE ACTIVITY

Erythrocyte pyrimidine-5'-nucleotidase (5'-ribonucleotide phosphohydrolase, E.C. 3.1.3.5, i.e., Py5N) catalyzes the hydrolytic dephosphorylation of the pyrimidine nucleotides uridine monophosphate (UMP) and cytidinemonophosphate (CMP) to uridine and cytidine (Paglia and Valentine, 1975). Enzyme inhibition by lead in humans and animals results in incomplete degradation of reticulocyte ribonucleic acid (RNA) fragments, accumulation of the nucleotides, and increased cell hemolysis (Paglia et al., 1975; Paglia and Valentine, 1975; Angle and McIntire, 1978; George and Duncan, 1982).

Two methods are available for measurement of Py5N activity. One is quite laborious in terms of time and manipulation, while the other is shorter but requires the use of radioisotopes and radiometric measurement. In Paglia and Valentine's (1975) method, heparinized venous blood was filtered through cotton or a commercial cellulose preparation to separate erythrocytes from platelets and leukocytes. Cells were given multiple saline washings, packed lightly, and subjected to freeze hemolysis. The hemolysates were dialyzed against a saline-Tris buffer containing $MgCl_2$ and EDTA to remove nucleotides and other phosphates. The assay system consists of dialyzed hemolysate, $MgCl_2$, Tris buffer at pH 8.0, and either UMP or CMP; incubation is for 2 hr at 37°C. Activity is terminated by treatment with 20 percent trichloroacetic acid, followed by centrifugation. The supernatant inorganic phosphate, P_i, is measured by the classic method of Fiske and Subbarow (1925), and the phosphomolybdic acid complex is measured spectrophotometrically at 660 nm. A unit of enzyme activity is expressed as μmol P_i/hr/g hemoglobin. Hemolysates appear to be stable (90 percent) with refrigeration at 4°C for up to 6 days, provided that mercaptoethanol is added at the time of assay. Like the other method, activity measurement requires the determination of hemoglobin.

In the simpler approach of Torrance et al. (1977), which can be feasibly applied to much larger numbers of samples, erythrocytes were separated from leukocytes and platelets with a 1:1 mixture of microcrystalline and alphacellulose, followed by saline washing and hemolysis with a solution of mercaptoethanol and EDTA. Hemolysates were incubated with a medium containing purified ^{14}C-CMP and $MgCl_2$ for 30 min at 37°C. The reaction was terminated by sequential addition of barium hydroxide and zinc sulfate solution. Proteins and unreacted nucleotide were precipitated, leaving the labeled cytidine in the supernatant. Aliquots were measured for ^{14}C-activity in a liquid scintillation counter. Enzyme activity was expressed as nM CMP/min/g hemoglobin. The blank activity was determined for each sample by carrying out the precipitation step as soon as the hemolysate was mixed with the labeled CMP, i.e., t = 0. This procedure shows a good correlation (r = 0.94; range: 135-189 enzyme units) with the method of Paglia and Valentine (1975). The two methods express units of enzyme activity differently, so that one must know which method is used when comparing enzyme activity.

9.8 MEASUREMENT OF PLASMA 1,25-DIHYDROXYVITAMIN D

The active form of vitamin D in bone mineral metabolism, including absorption of calcium and phosphorus as well as bone resorption of these minerals, is the hormonal metabolite, 1,25-dihydroxyvitamin D (1,25-$(OH)_2$D). Given the growing interest in the adverse effects of lead on the biosynthesis of this crucial metabolite (see Chapters 10, 12 and 13), a brief discussion of the quantitative measurement of this metabolite is merited. Techniques for measurement of 1,25-$(OH)_2$D are all of recent vintage, are all rather lengthy procedurally, and all require a rather high level of laboratory expertise and proficiency.

Reported methodology, whatever the differences in specific details, can be broken down into three discrete steps: (1) isolation of the metabolite from plasma or serum by liquid-liquid extraction using solvents common in lipid analysis; (2) preconcentration of the extracts and chromatographic purification using Sephadex LH-20 or Lipidex 5000 columns along with, in some cases, HPLC; and (3) subsequent quantitation by either of two radiometric binding techniques: the more common competitive protein binding (CPB) assay or radioimmunoassay (RIA). The CPB assay normally involves the use of a receptor protein in the intestinal cytosol of chicks made vitamin D-deficient.

Most illustrative of 1,25-$(OH)_2$D measurement is the technique of Shepard et al. (1979), which also includes steps for the analysis of other metabolites not discussed here. Human plasma, 3-5 ml, to which tritiated metabolite is added as tracer internal standard, is extracted with a mixture of methanol and methylene chloride, followed by separation of the $(OH)_2D$ fraction (to include the 24,25- and 25,26-$(OH)_2$ metabolites) from other metabolites using a Sephadex LH-20 column. Subsequent use of HPLC (straight phase, Zorbax-SIL) separates the 1,25-$(OH)_2$ metabolite from the other two dihydroxylated products. Quantification is by CPB assay. In human adults, the mean metabolite level is 31 picograms/ml. Limit of detection is 5 picograms/analytical tube, mean recovery is 58.4 percent, and the within-run and between-run coefficients of variation are 17 and 26 percent, respectively.

Two interlaboratory surveys of methodology for vitamin D metabolite analysis have recently been described (Jongen et al., 1982; Jongen et al., 1984). In the more recent and comprehensive of the two (Jongen et al., 1984), 15 laboratories carried out analyses of eight plasma samples and two standards for 1,25-$(OH)_2D$. Mean interlaboratory coefficient of variation for analysis of 1,25-$(OH)_2D$ in the plasma samples was 52 percent. In this survey, nine laboratories used the CPB assay, with six using RIA for quantitation. The major reason, however, for the variance appeared to be differences in methods of purification. The upshot of this survey is that results for a given sample will vary with specifics of procedure. Thus each laboratory should establish its own reference values.

9.9 SUMMARY

A complete understanding of a toxic agent's biological effects (including any statement of dose-effect relationships) requires quantitative measurement of either that agent in some biological medium or a physiological parameter associated with exposure to the agent. Quantitative analysis involves a number of discrete steps, all of which contribute to the overall reliability of the final analytical result: sample collection and shipment, laboratory handling, instrumental analysis, and criteria for internal and external quality control.

From a historical perspective, the definition of "satisfactory analytical method" for lead has been changing steadily as new and more sophisticated equipment has become available and understanding of the hazards of pervasive contamination along the analytical course has increased. The best example of this change is the current use of the definitive method for lead analysis, isotope-dilution mass spectrometry (IDMS) in tandem with "ultra-clean" facilities and sampling methods, to demonstrate conclusively not only the true extent of anthropogenic input of lead to the environment over the years but also the relative limitations of most of the methods used today for lead measurement.

9.9.1 Determinations of Lead in Biological Media

The low levels of lead in biological media, even in the face of excessive exposure, and the fact that sampling of such media must be done against a backdrop of pervasive lead contamination necessitates that samples be collected and handled carefully. Blood lead sampling is best done by venous puncture and collection into low-lead tubes after careful cleaning of the puncture site. The use of finger puncture as an alternative method of sampling should be avoided, if feasible, given the risk of contamination associated with the practice in industrialized areas. While collection of blood onto filter paper enjoyed some popularity in the past, paper deposition of blood requires special correction for hematocrit/hemoglobin level.

Urine sample collection requires the use of lead-free containers as well as addition of a bactericide. If feasible, 24-hr sampling is preferred to spot collection. Deciduous teeth vary in lead content both within and across type of dentition. Thus, a specific tooth type should be uniformly obtained for all study subjects and, if possible, more than a single sample should be obtained from each subject.

Measurements of Lead in Blood. Many reports over the years have purported to offer satisfactory analysis of lead in blood and other biological media, often with severe inherent limitations on accuracy and precision, meager adherence to criteria for accuracy and precision, and a limited utility across a spectrum of analytical applications. Therefore, it is only useful to discuss "definitive" and, comparatively speaking, "reference" methods currently in use.

In the case of lead in biological media, the definitive method is isotope-dilution mass spectrometry (IDMS). The accuracy and unique precision of IDMS arise from the fact that all manipulations are on a weight basis involving simple procedures, and measurements entail only lead isotope ratios and not the absolute determinations of the isotopes involved, which greatly reduces instrumental corrections and errors. Reproducible results to a precision of one part in 10^4-10^5 are routine with appropriately designed and competently operated instrumentation. Although this methodology is still not recognized in many laboratories, it was the first breakthrough, in tandem with "ultra-clean" procedures and facilities, in definitive methods for indexing the progressive increase in lead contamination of the environment over the centuries. Given the expense, required level of operator expertise, and time and effort involved for measurements by IDMS, this method mainly serves for analyses that either require extreme accuracy and precision, e.g., geochronometry, or for the establishment of analytical reference material for general testing purposes or the validation of other methodologies.

While the term "reference method" for lead in biological media cannot be rigorously applied to any procedures in popular use, the technique of atomic absorption spectrometry (AAS) in its various configurations, or the electrochemical method, anodic stripping voltammetry (ASV), come closest to meriting the designation. Other methods that are generally applied in metal analyses are either limited in sensitivity or are not feasible for use on theoretical grounds for lead analysis.

AAS, as applied to analysis of whole blood, generally involves flame or flameless micromethods. One macromethod, the Hessel procedure, still enjoys some popularity. Flame microanalysis, the Delves cup procedure, applied to blood lead appears to have an operational sensitivity of about 10 µg/dl blood and a relative precision of approximately 5 percent in the range of blood lead seen in populations in industrialized areas. The flameless, or electrothermal, method of AAS enhances sensitivity about tenfold, but precision can be more problematic because of chemical and spectral interferences.

The most widely used and sensitive electrochemical method for lead in blood is ASV. For the most accurate results, chemical wet ashing of samples must be carried out, although this process is time-consuming and requires the use of lead-free reagents. The use of metal exchange reagents has been employed in lieu of the ashing step to liberate lead from binding sites, although this substitution is associated with less precision. For the ashing method, relative precision is approximately 5 percent. In terms of accuracy and sensitivity, problems appear at low levels, e.g., 5 µg/dl or below, particularly if samples contain elevated copper levels.

Lead in Plasma. Since lead in whole blood is virtually all confined to the erythrocyte, plasma levels are quite low and extreme care must be employed to measure plasma levels reliably. The best method for such measurement is IDMS, in tandem with ultra-clean facility use. AAS is satisfactory for comparative analyses across a range of relatively high whole blood values.

Lead in Teeth. Lead measurement in teeth has involved either whole tooth sampling or analysis of specific regions, such as dentine or circumpulpal dentine. In either case, samples must be solubilized after careful surface cleaning to remove contamination; solubilization is usually accompanied by either wet ashing directly or ashing subsequent to a dry ashing step.

AAS and anodic stripping have been employed more frequently for such determinations than any other method. With AAS, the high mineral content of teeth argues for preliminary isolation of lead via chelation/extraction. The relative precision of analysis for within-run measurement is around 5-7 percent, with the main determinant of variance in regional assay being the initial isolation step. One change from the usual methods for such measurement is the *in situ* measurement of lead by X-ray fluorescence spectrometry in children. Lead measured in this fashion allows observation of ongoing lead accumulation, rather than waiting for exfoliation.

Lead in Hair. Hair as an exposure indicator for lead offers the advantages of being noninvasive and a medium of indefinite stability. However, the crucial problem of external surface contamination is such that it is still not possible to state that any cleaning protocol reliably differentiates between externally and internally deposited lead.

Studies that demonstrate a correlation between increasing hair lead and increasing severity of a measured effect tend to support arguments for using hair as an external indicator of exposure. Probably, then, such measurement using cleaning protocols that have not been independently validated will overstate the relative accumulation of "internal" hair lead in terms of some endpoint and will also underestimate the relative sensitivity of changes in internal lead content with exposure. One consequence of this would be, for example, an apparent threshold for a given effect in terms of hair lead which is significantly above the actual threshold. Because of these concerns, hair is best used with the simultaneous measurement of blood lead.

Lead in Urine. Analysis of lead in urine is complicated by the relatively low levels of the element in this medium as well as the complex mixture of mineral elements present. Urine lead levels are most useful and also somewhat easier to determine in cases of chelation mobilization or chelation therapy, where levels are high enough to permit good precision and dilution of matrix interference.

Samples are probably best analyzed by prior chemical wet ashing, using the usual mixture of acids. Both ASV and AAS have been applied to urine analysis, with the latter more routinely used and usually with a chelation/extraction step.

Lead in Other Tissues. Bone samples require cleaning procedures for removal of muscle and connective tissue and chemical solubilization prior to analysis. Methods of analysis are comparatively limited and flameless AAS is the technique of choice.

In vivo lead measurements in bone of lead workers have been reported using X-ray fluorescence analysis and a radioisotopic source for excitation. One problem with this approach with moderate lead exposure is the detection limit, approximately 20 ppm. Soft organ analysis poses a problem in terms of heterogeneity in lead distribution within an organ (e.g., brain and kidney). In such cases, regional sampling or homogenization must be carried out. Both flame and flameless AAS appear to be satisfactory for soft tissue analysis and are the most widely used.

Quality Assurance Procedures in Lead Analyses. In terms of available information, the major focus in establishing quality control protocols for lead has involved whole blood measurements. Translated into practice, quality control revolves around steps employed within the laboratory, using a variety of internal checks, and the further reliance on external checks, such as a formal continuing multi-laboratory proficiency testing program.

Within the laboratory, quality assurance protocols can be divided into start-up and routine procedures, the former involving establishment of detection limits, within-run and between-run precision, analytical recovery, and comparison with some reference technique within or outside the laboratory. The reference method is assumed to be accurate for the particular level of lead in some matrix at a particular point in time. Correlation with such a method at a satisfactory level, however, may simply indicate that both methods are equally inaccurate but performing with the same level of precision proficiency. More preferable is the use of certified samples having lead at a level established by the definitive method.

For blood lead, the Centers for Disease Control (CDC) periodically survey overall accuracy and precision of methods used by reporting laboratories. In terms of overall accuracy and precision, one such survey found that ASV as well as the Delves cup and extraction variations of AAS performed better than other procedures. These results do not mean that a given laboratory cannot perform better with a particular technique; rather, such data are of assistance for new facilities choosing among methods.

Of particular value to laboratories carrying out blood lead analysis are the external quality assurance programs at both the State and Federal levels. The most comprehensive proficiency testing program is that carried out by the CDC. This program actually consists of two subprograms, one directed at facilities involved in lead poisoning prevention and screening (Center for Environmental Health) and the other concerned with laboratories seeking certification under the Clinical Laboratories Improvement Act of 1967 as well as under regulations of the Occupational Safety and Health Administration's (OSHA) Laboratory Improvement Program Office. Judging from the relative overall improvements in reporting laboratories over the years of the programs' existence, the proficiency testing programs have served their purpose well. In this regard, OSHA criteria for laboratory certification require that eight of nine samples be analyzed correctly for the previous quarter. This level of required proficiency reflects the ability of a number of laboratories to actually perform at this level.

9.9.2 Determination of Erythrocyte Porphyrin (Free Erythrocyte Protoporphyrin, Zinc Protoporphyrin)

With lead exposure, erythrocyte protoporphyrin IX accumulates because of impaired placement of divalent iron to form heme. Divalent zinc occupies the place of the native iron. Depending upon the method of analysis, either metal-free erythrocyte porphyrin (EP) or zinc protoporphyrin (ZPP) is measured, the former arising from loss of zinc in the chemical manipulation. Virtually all methods now in use for EP analysis exploit the ability of the porphyrin to undergo intense fluorescence when excited by ultraviolet light. Such fluorometric methods can be further classified as wet chemical micromethods or direct measuring fluorometry using the hematofluorometer. Because of the high sensitivity of such measurement, relatively small blood samples are required, with liquid samples or blood collected on filter paper.

The most common laboratory or wet chemical procedures now in use represent variations of several common chemical procedures: (1) treatment of blood samples with a mixture of ethyl acetate/acetic acid followed by a repartitioning into an inorganic acid medium, or (2) solubilization of a blood sample directly into a detergent/buffer solution at a high dilution. Quantification has been done using protoporphyrin, coproporphyrin, or zinc protoporphyrin IX plus pure zinc ion. The levels of precision for these laboratory techniques vary somewhat with the specifics of analysis. The Piomelli method has a coefficient of variation of 5 percent, while the direct ZPP method using buffered detergent solution is higher and more variable.

The recent development of the hematofluorometer has made it possible to carry out EP measurements in high numbers, thereby making population screening feasible. Absolute calibration is necessary and requires periodic adjustment of the system using known concentrations of EP in reference blood samples. Since these units are designed for oxygenated blood (i.e., capillary blood), use of venous blood requires an oxygenation step, usually a moderate shaking for several minutes. Measurement of low or moderate levels of EP can be affected by interference with bilirubin. Competently employed, the hematofluorometer is reasonably precise, showing a total coefficient of variation of 4.11-11.5 percent. While the comparative accuracy of the unit has been reported to be good relative to the reference wet chemical technique, a very recent study has shown that commercial units carry with them a significant negative bias, which may lead to false negatives in subjects having only moderate EP elevation. Such a bias in accuracy has been difficult to detect in existing EP proficiency testing programs. By comparison to wet methods, the hematofluorometer should be restricted to field use rather than becoming a substitute in the laboratory for chemical measurement, and this field use should involve periodic split-sample comparison testing with the wet method.

9.9.3 Measurement of Urinary Coproporphyrin

Although EP measurement has largely supplanted the use of urinary coproporphyrin (CP-U) analysis to monitor excessive lead exposure in humans, this measurement is still of value in that it reflects active intoxication. The standard analysis is a fluorometric technique, whereby urine samples are treated with buffer, and an oxidant (iodine) is added to generate CP from its precursor. The CP-U is then partitioned into ethyl acetate and re-extracted with dilute hydrochloric acid. The working curve is linear below 5 μg CP/dl urine.

9.9.4 Measurement of Delta-Aminolevulinic Acid Dehydrase Activity

Inhibition of the activity of the erythrocyte enzyme delta-aminolevulinic acid dehydrase (ALA-D) by lead is the basis for using such activity in screening for excessive lead exposure. A number of sampling and sample handling precautions attend such analysis. Since zinc (II) ion will offset the degree of activity inhibition by lead, blood collecting tubes must have extremely low zinc content, which essentially rules out the use of rubber-stoppered blood tubes. Enzyme instability necessitates that the activity measurement be carried out within 24 hr of blood collection. Porphobilinogen, the product of enzyme action, is light labile and requires the assay be done in restricted light. Various procedures for ALA-D measurement are based on measurement of the level of the chromophoric pyrrole (approximately 555 nm) formed by condensation of the porphobilinogen with p-dimethylaminobenzaldehyde.

In the European Standardized Method for ALA-D activity determination, blood samples are hemolyzed with water, ALA solution added, followed by incubation at 37°C, and the reaction terminated by a solution of mercury (II) in trichloroacetic acid. Filtrates are treated with modified Ehrlich's reagent (p-dimethylaminobenzaldehyde) in trichloroacetic/perchloroacetic acid mixture. Activity is quantified in terms of micromoles δ-ALA/min·l erythrocytes.

One variation in the above procedure is the initial use of a thiol agent, such as dithiothreotol, to reactivate the enzyme, giving a measure of the full native activity of the enzyme. The ratio of activated/unactivated activity versus blood lead levels accommodates genetic differences between individuals.

9.9.5 Measurement of Delta-Aminolevulinic Acid in Urine and Other Media

Levels of delta-aminolevulinic acid (δ-ALA) in urine and plasma increase with elevated lead exposure. Thus, measurement of this metabolite, generally in urine, provides an index of the level of lead exposure. ALA content of urine samples (ALA-U) is stable for about 2 weeks or more with sample acidification and refrigeration. Levels of ALA-U are adjusted for urine density or expressed per unit creatinine. If feasible, 24-hr collection is more desirable than spot sampling.

Virtually all the various procedures for ALA-U measurement employ preliminary isolation of ALA from the balance of urine constituents. In one method, further separation of ALA from the metabolite aminoacetone is done. Aminoacetone can interfere with colorimetric measurement. ALA is recovered, condensed with a beta-dicarbonyl compound, e.g., acetyl acetone, to yield a pyrrole intermediate. This intermediate is then reacted with p-dimethylaminobenzaldehyde in perchloric/acetic acid, followed by colorimetric reading at 553 nm. In one variation of the basic methodology, ALA is condensed with ethyl acetoacetate directly and the resulting pyrrole extracted with ethyl acetate. Ehrlich's reagent is then added as in other procedures and the resulting chromophore is measured spectrophotometrically.

Measurement of ALA in plasma is much more difficult than in urine, since plasma ALA is at nanogram/milliliter levels. In one gas-liquid chromatographic procedure, ALA is isolated from plasma, reacted with acetyl acetone and partitioned into a solvent that also serves for pyrolytic methylation of the involatile pyrrole in the injector port of the chromatograph, making the derivative more volatile. For quantification, an internal standard, 6-amino-5-oxohexanoic acid, is used. While the method is more involved, it is more specific than the older colorimetric technique.

9.9.6 Measurement of Pyrimidine-5'-Nucleotidase Activity

Erythrocyte pyrimidine-5'-nucleotidase (Py5N) activity is inhibited with lead exposure. Currently, two different methods are used for assaying the activity of this enzyme. The older method is quite laborious in time and effort, whereas the more recent approach is shorter but uses radioisotopes and radiometric measurement.

In the older method, heparinized venous blood is filtered through cellulose to separate erythrocytes from platelets and leukocytes. Cells are then freeze-fractured and the hemolysates dialyzed to remove nucleotides and other phosphates. This dialysate is then incubated in the presence of a nucleoside monophosphate and cofactors, the enzyme reaction being terminated by treatment with trichloroacetic acid. The inorganic phosphate isolated from added substrate is measured colorimetrically as the phosphomolybdic acid complex.

In the radiometric assay, hemolysates obtained as before are incubated with pure ^{14}C-CMP. By addition of a barium hydroxide/zinc sulfate solution, proteins and unreacted nucleotide are precipitated, leaving labeled cytidine in the supernatant. Aliquots are measured for ^{14}C activity in a liquid scintillation counter. This method shows a good correlation with the earlier technique.

9.9.7 Measurement of Plasma 1,25-Dihydroxyvitamin D

Measurement techniques for this vitamin D metabolite, all of recent vintage, consist of three main parts: (1) isolation from plasma or serum by liquid-liquid extraction, (2) preconcentration of the extract and chromatographic purification using Sephadex LH-20 or Lipidex 5000 columns, as well as high performance liquid chromatography (HPLC) in some cases, and (3) quantification by either of two radiometric binding techniques, the more common competitive protein binding (CPB) assay or radioimmunoassay (RIA). The CPB assay uses a receptor protein in intestinal cytosol of chicks made vitamin D-deficient.

In one typical study, human adults had a mean level of 31 picograms/ml. The limit of detection was 5 picograms/analytical tube, and within-run and between-run coefficients of variation were 17 and 26 percent, respectively. In a recent interlaboratory survey involving 15 laboratories, the level of variance was such that it was recommended that each laboratory should establish its own reference values.

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10. METABOLISM OF LEAD

10.1 INTRODUCTION

This chapter examines the absorption, distribution, retention, and excretion of lead in humans and animals and the various factors that mediate the extent of the toxicokinetic processes of lead. While inorganic lead is the form of the element that has been most heavily studied, organolead compounds are also emitted into the environment and, because they are quite toxic, they are also included in the discussion. Since the preparation of the 1977 Air Quality Criteria Document for Lead (U.S. Environmental Protection Agency, 1977), a number of reports have appeared that have proven particularly helpful in both quantifying the various processes to be discussed in this chapter and assessing the interactive impact of factors such as nutritional status in determining internal exposure risk.

10.2 LEAD ABSORPTION IN HUMANS AND ANIMALS

The amounts of lead entering the bloodstream from various routes of absorption are determined not only by the levels of the element in the particular media, but also by the various physical and chemical parameters that characterize lead. Furthermore, specific host factors such as age and nutritional status are important, as is interindividual variability. Additionally, to assess absorption rates, one must know whether or not the subject is in "equilibrium" with respect to a given level of lead exposure.

10.2.1 Respiratory Absorption of Lead

The movement of lead from ambient air to the bloodstream is a two-part process: a fraction of air lead is deposited in the respiratory tract and, of this deposited amount, some fraction is subsequently absorbed directly into the bloodstream or otherwise cleared from the respiratory tract. At present, enough data exist to make some quantitative statements about both of these components of respiratory absorption of lead.

The 1977 Air Quality Criteria Document for Lead described the model of the International Radiological Protection Commission (IRPC) for the deposition and removal of lead from the lungs and the upper respiratory tract (International Radiological Protection Commission, 1966). Briefly, the model predicts that 35 percent of lead inhaled from ambient air by humans is deposited in the respiratory tract, with most of the lead going to the parenchyma and airways. The IRPC model predicts a total deposition of 40-50 percent for particles with a mass median aerodynamic diameter (MMAD) of 0.5 μm and indicates that the absorption rate would vary depending on the solubility of the particular form. More recent data on lead deposition modeling, however, provide a more precise picture (see next section).

10.2.1.1 Human Studies. Table 10-1 tabulates the various studies of human subjects that provide data on the deposition of inorganic lead in the respiratory tract. Studies of this type have used diverse methodologies to characterize the inhaled particles in terms of both size (and size ranges) and fractional distribution. The use of radioactive or stable lead isotopes to directly or indirectly measure lead deposition and uptake into the bloodstream has been particularly helpful in quantifying these processes.

From the studies of Kehoe (1961a,b,c) and their update by Gross (1981), as well as data from Chamberlain et al. (1978), Morrow et al. (1980), and Nozaki (1966), the respiratory deposition of airborne lead as encountered in the general population appears to be approximately 30-50 percent, depending on particle size and ventilation rates. Ventilation rate is particularly important with submicrometer particles, where Brownian diffusion governs deposition, because a slower breathing rate enhances the frequency of collisions of particles with the alveolar wall.

Figure 10-1 (Chamberlain et al., 1978) compares data, both calculated and experimentally measured, on the relationship of percentage deposition to particle size. As particle size increases, deposition rate decreases to a minimum over the range where Brownian diffusion predominates. Subsequently, deposition increases with size (>0.5 μm MMAD) as impaction and sedimentation become the main deposition factors.

In contrast to the ambient air or chamber data tabulated in Table 10-1, higher deposition rates in some occupational settings are associated with relatively large particles. However, much of this deposition is in the upper respiratory tract, with eventual movement to the gastrointestinal tract by ciliary action and swallowing. Mehani (1966) measured total deposition rates of 28-70 percent in battery workers and workers in marine scrap yards. Chamberlain and Heard (1981) calculated an absorption rate of approximately 47 percent for particle sizes encountered in workplace air.

Systemic absorption of lead from the lower respiratory tract occurs directly, while much of the absorption from the upper tract involves swallowing and some uptake in the gut. From the radioactive isotope data of Chamberlain et al. (1978) and Morrow et al. (1980), and the stable isotope studies of Rabinowitz et al. (1977), one can conclude that lead deposited in the lower respiratory tract is totally absorbed.

Chamberlain et al. (1978) used ^{203}Pb in engine exhaust, lead oxide, or lead nitrate aerosols in experiments where human subjects inhaled the lead from a chamber through a mouthpiece or in wind-tunnel aerosols. By 14 days, approximately 90 percent of the label was removed from the lung. Lead movement into the bloodstream could not be described by a simple exponential function; 20 percent was absorbed within 1 hr and 70 percent within 10 hr.

TABLE 10-1. DEPOSITION OF LEAD IN THE HUMAN RESPIRATORY TRACT

Form	Particle size	Lead Exposure	Percent deposition	Reference
Pb_2O_3 aerosols from engine exhaust	0.05 µm median count diameter in 38 studies; 5 subjects exposed to average of 0.9 µm	Chamber studies; 10, 20, or 150 $\mu g/m^3$; 3 hr on alternate days; 12 subjects	30-70% (mean: 48%) for mainly 0.05-µm particles	Kehoe (1961a,b,c); Gross (1981)
Lead "fumes" made in induction furnace	0.05-1.0 µm mean diameter	Mouthpiece/aerosol chamber; 10 mg/m^3; adult subjects	42% 0.05 µm; 63% 1.0 µm	Nozaki (1966)
$^{203}Pb_2O_3$ aerosol	Mean densities of 0.02, 0.04, 0.09 µm	Mouthpiece/aerosol chamber; adult subjects	80% 0.02 µm; 45% 0.04 µm; 30% 0.09 µm	Chamberlain et al. (1978)
Ambient air lead near motorway and other urban areas in U.K.	Mainly 0.1 µm	2-10 $\mu g/m^3$; adult subjects	60% fresh exhaust; 50% other urban area	Chamberlain et al. (1978)
$^{203}Pb(OH)_2$ or $^{203}PbCl_2$ aerosols	Both forms at 0.25 µm MMAD	0.2 µCi/liter for 5 min or ≤50 liters air; adult subjects	23% chloride; 26% hydroxide	Morrow et al. (1980)
Lead in workplace air; battery factory and shipbreaking operations	Not determined; defined as fumes, fine dust, or coarse dust	3 adult groups: 23 $\mu g/m^3$ - controls 86 $\mu g/m^3$ - battery workers 180 $\mu g/m^3$ - scrap yard workers	47% battery workers; 39% shipyard and controls	Mehani (1966)

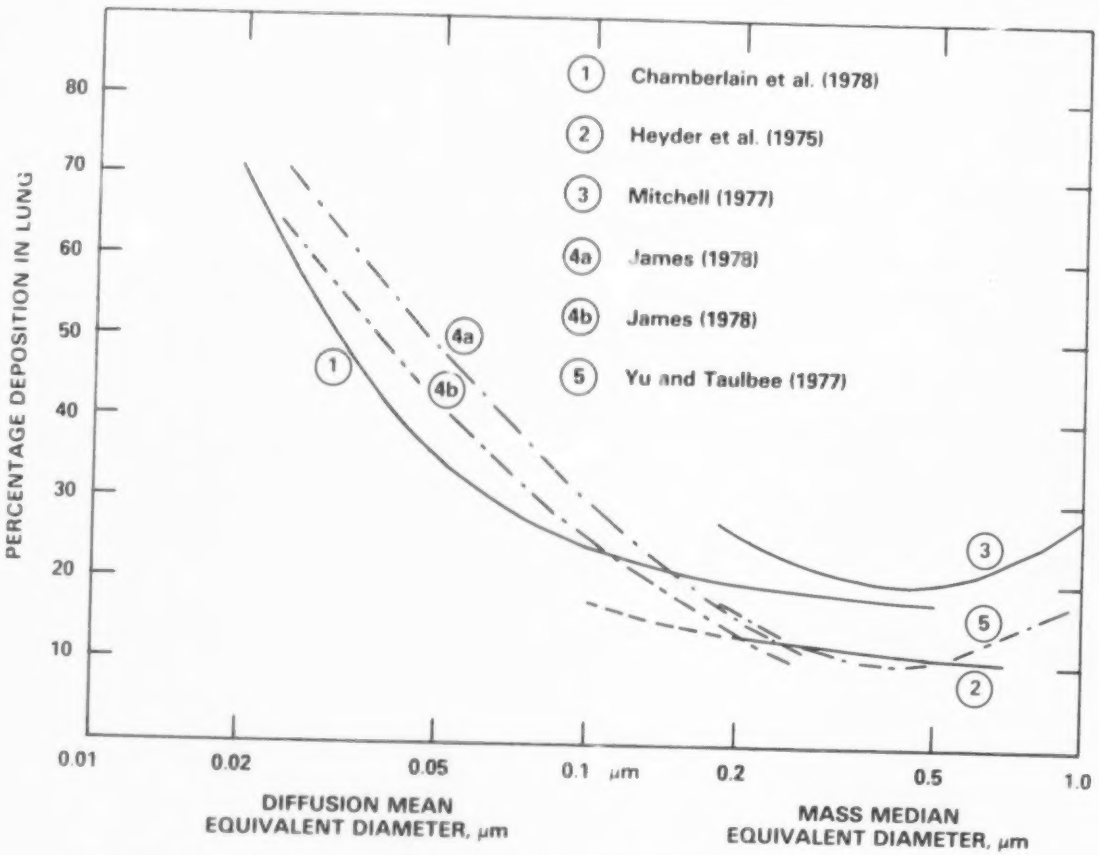


Figure 10-1. Effect of particle size on lead deposition rate in the lung. Broken lines derived by calculation from reported data. Tidal volume equals 1000 cm³ except for line 4b, where it equals 500 cm³. Breathing cycle equals 4 sec.

Source: Chamberlain et al. (1978).

Rabinowitz et al. (1977) administered ^{204}Pb tracer to adult volunteers and determined (by isotope tracer and balance data) that 14 µg lead was absorbed by these subjects daily at ambient air lead levels of 1-2 µg/m^3. Assuming a daily ventilation rate of 20 m^3, a deposition rate of 50 percent of ambient air (Chamberlain et al., 1978), and a mean air lead level of 1.5 µg/m^3 (2.0 µg/m^3 outside the study unit, 1.0 µg/m^3 inside, as determined by the authors), then 15 µg lead was available for absorption. Hence, better than 90 percent of deposited lead was absorbed daily.

Morrow et al. (1980) followed the systemic uptake of ^{203}Pb in 17 adult subjects using either lead chloride or lead hydroxide aerosols with an average size of 0.25 (±0.1) µm MMAD. Half of the deposited fraction of either aerosol was absorbed in 14 hr or less. The radiolabel data described above are consistent with the data of Hursh and Mercer (1970), who studied the systemic uptake of ^{212}Pb on a carrier aerosol.

Given the apparent invariance of absorption rate for deposited lead in the above studies as a function of the chemical form of the element (Chamberlain et al., 1978; Morrow et al., 1980), inhaled lead lodging deep in the respiratory tract seems to be absorbed equally, regardless of form. Supporting evidence for total human systemic uptake of lead comes from autopsy tissue analysis for lead content. Barry (1975) found that lead was not accumulated in the lungs of lead workers. This observation is corroborated by the data of Gross et al. (1975) for nonoccupationally exposed subjects.

Dependence of the respiratory absorption rate for lead in humans on the level of lead in air has not been extensively studied, although the data of Chamberlain and coworkers (1978), using human volunteers, show that the lung clearance rate in the adult for single lead pulses did not vary over a lung burden range of 0.3 to 450 µg. In occupational settings, a curvilinear relationship between workplace airborne lead and blood lead results at least partly from particle size changes, i.e., with increasing dust concentration, particle aggregation rate increases and the effective fraction of submicron particles (those penetrating to the lung) compared to total particles steadily lessens (Chamberlain, 1983).

All of the available data for lead deposition and uptake from the respiratory tract in humans have been obtained with adults, and quantitative comparisons with the same exposures in children are not possible. Although children 2 years of age weigh one-sixth as much as an adult, they inhale 40 percent as much air lead as adults (Barltrop, 1972). James (1978) has taken into account differences in airway dimensions in adults versus children, and has estimated that, after controlling for weight, the 10-year-old child has a deposition rate 1.6- to 2.7-fold higher than the adult.

Recent studies support the above estimates of James (1978). Hofmann and coworkers (Hofmann, 1982; Hofmann et al., 1979) reported dose calculations for the respiratory tract as a function of age using airway length estimates from the literature and determined that intake of radioactive nuclides into both the tracheobronchial and pulmonary regions was highly age-dependent, with maximal intake occurring at about age six.

10.2.1.2 Animal Studies. Experimental animal data for quantitative assessment of lead deposition and absorption for the lung and upper respiratory tract are limited. The available information does, however, support the finding that respired lead is extensively and rapidly absorbed.

Morgan and Holmes (1978) exposed adult rats, by nose-only technique, to a ^{203}Pb-labeled engine exhaust aerosol generated in the same manner as by Chamberlain et al. (1978) over a period of 8 days. Exposure was at a level of 21.9 to 23.6 nCi label/liter chamber air. Adjusting for deposition on the animal pelt, 20-25 percent of the label was deposited in the lungs. Deposited lead was taken up extensively in blood (50 percent within 1 hr and 98 percent within 7 days). The absorption-rate kinetic profile was similar to that reported for humans (Chamberlain et al., 1978).

Boudene et al. (1977) exposed rats to ^{210}Pb-labeled aerosols at a level of 1 μg label/m^3 and 10 μg label/m^3, the majority of the particles being 0.1-0.5 μm in size. At 1 hr, 30 percent of the label had left the lung; by 48 hr, 90 percent was gone.

Bianco et al. (1974) used ^{212}Pb aerosol (≤0.2 μm) inhaled briefly by dogs and found a clearance half-time from the lung of approximately 14 hr. Greenhalgh et al. (1979) found that direct instillation of ^{203}Pb-labeled lead nitrate solution into the lungs of rats led to an uptake of approximately 42 percent within 30 min, compared with an uptake rate of 15 percent within 15 min in the rabbit. These instillation data are consistent with the report of Pott and Brockhaus (1971), who noted that intratracheal instillation of lead in solution (as bromide) or in suspension (as oxide) serially over 8 days resulted in systemic lead levels in tissues indistinguishable from injected lead levels. Rendall et al. (1975) found that the movement of lead into blood of baboons inhaling a lead oxide (Pb_3O_4) was more rapid and resulted in higher blood lead levels when coarse (1.6 μm mean diameter) rather than fine (0.8 μm mean diameter) particles were used.

10.2.2 Gastrointestinal Absorption of Lead

Gastrointestinal (GI) absorption of lead mainly involves uptake from food and beverages, as well as lead deposited in the upper respiratory tract that is eventually swallowed. It also includes ingestion of nonfood material, primarily in children via normal mouthing activity and pica. Two issues of concern with lead uptake from the gut are the comparative rates of such absorption in developing versus adult organisms, including humans, and how the bioavailability of lead affects such uptake.

10.2.2.1 Human Studies. Based on long-term metabolic studies with adult volunteers, Kehoe (1961a,b,c) estimated that approximately 10 percent of dietary lead is absorbed from the human gut. According to Gross (1981), various balance parameters can vary considerably among subjects. These studies (Kehoe, 1961a,b,c) did not take into account the contribution of biliary clearance of lead into the gut, which would have affected measurements for both absorption and total excretion. Chamberlain et al. (1978) determined that the level of endogenous fecal lead is approximately 50 percent of urinary lead values. They have estimated that 15 percent of dietary lead is absorbed, if the amount of endogenous fecal lead is taken into account.

Following the Kehoe studies, a number of reports determined GI absorption using both stable and radioisotopic labeling of dietary lead. Generally, these reports support the observation that in the adult human the absorption of lead is limited when taken with food. Harrison et al. (1969) determined a mean absorption rate of 14 percent for three adult subjects ingesting ^{203}Pb in diet, a figure in accord with the results of Hursh and Suomela (1968). Chamberlain et al. (1978) studied the absorption of ^{203}Pb in two forms (as the chloride and as the sulfide) taken with food. The corresponding absorption rates were 6 percent (sulfide) and 7 percent (chloride), taking into account endogenous fecal excretion. Using adult subjects who ingested the stable isotope ^{204}Pb in their diet, Rabinowitz et al. (1974) reported an average gut absorption of 7.7 percent. In a later study, Rabinowitz et al. (1980) measured an absorption rate of 10.3 percent.

A number of recent studies indicate that lead ingested under fasting conditions is absorbed to a much greater extent than lead taken with or incorporated into food. For example, Blake (1976) measured a mean absorption rate of 21 percent when 11 adult subjects ingested ^{203}Pb-labeled lead chloride several hours after breakfast. Chamberlain et al. (1978) found that lead uptake in six subjects fed ^{203}Pb as the chloride was 45 percent after a fasting period, compared to 6 percent with food. Heard and Chamberlain (1982) obtained a rate of 63.3 percent using a similar procedure with eight subjects. Rabinowitz et al. (1980) reported an absorption rate of 35 percent in five subjects when ^{204}Pb was ingested after 16 hr of fasting. These isotope studies support the observations of Barltrop (1975) and Garber and Wei (1974) that lead in between-meal beverages is absorbed to a greater extent than is lead in food.

Dependence of the lead absorption rate from the human GI tract on the concentration of lead in diet or water has not been well studied. Recent data from the reports of Blake (1980), Flanagan et al. (1982), and Heard and Chamberlain (1983), however, indicate little concentration dependency across the range of dietary lead content encountered by the general population. For example, Flanagan et al. (1982) found that human volunteers absorbed 4, 40, and 400 μg of ingested lead at about the same rate.

The relationship of lead bioavailability in the human gut to the chemical/biochemical form of lead can be determined from available data, although interpretation is complicated by the relatively small amounts administered and the presence of various components of food already present in the gut. Harrison et al. (1969) found no difference in lead absorption from the human gut when lead isotope was given either as the chloride or incorporated into alginate. Chamberlain et al. (1978) found that labeled lead as the chloride or sulfide was absorbed to the same extent when ingested with food, but the sulfide form was absorbed at a rate of 12 percent compared with 45 percent for the chloride under fasting conditions. Rabinowitz et al. (1980) obtained similar absorption rates for the chloride, sulfide, or cysteine complex forms when administered with food or under fasting conditions. Heard and Chamberlain (1982) found no difference in absorption rate when isotopic lead (^{203}Pb) was ingested with unlabeled meat (sheep's liver and kidney) or when the label was incorporated into the food prior to slaughter.

The data of Moore et al. (1979) are of interest with respect to relative GI uptake of lead in adult males and females. Human volunteers (seven males, four females) were given ^{203}Pb in water and whole-body counting was carried out at time points. It appeared that females absorbed somewhat more of the label than males, but the difference did not reach statistical significance.

Two reports have focused on the question of differences in GI absorption rates between adults and children. Alexander et al. (1973) carried out 11 balance studies with eight children, aged 3 months to 8 years. Daily intake averaged 10.6 µg Pb/kg body weight (range 5-17). The mean absorption rate determined from metabolic balance studies was 53 percent. A two-part investigation by Ziegler et al. (1978) comprised a total of 89 metabolic balance studies with 12 normal infants aged 2 weeks to 2 years. In the first part, 51 balance studies using 9 children furnished a mean absorption rate of 42.7 percent. In the second, six children were involved in 38 balance studies involving dietary lead intake at 3 levels. Diets were closely controlled and lead content was measured. For all daily intakes of 5 µg Pb/kg or higher, the mean absorption rate was 42 percent. At low levels of lead intake the data were variable, with some children apparently in negative balance, probably because of the difficulty in controlling low lead intake.

In contrast to these reports, Barltrop and Strehlow (1978) found that the results for children hospitalized as orthopedic or "social" admissions were highly variable. A total of 104 balance studies were carried out in 29 children ranging in age from 3 weeks to 14 years. Fifteen of the subjects were in net negative balance, with an average dietary absorption of -40 percent or, when weighted by number of balance studies, -16 percent. Closely comparing these data with those of Ziegler et al. (1978) is difficult. Subjects were inpatients, represented a much greater age range, and were not classified in terms of mineral nutrition or weight-change status. As an urban pediatric group, the children in this study may have had higher prior lead exposure so that the "washout" phenomenon (Kehoe, 1961a,b,c; Gross, 1981) may have contributed to the highly variable results. The calculated mean daily lead intake in the Barltrop and Strehlow group (6.5 μg/kg) was lower than that for all but one study group described by Ziegler et al. (1978). In the latter study, data for absorption became more variable as the daily lead intake was lowered. Finally, in those children classified as orthopedic admissions, whether skeletal trauma was without effect on lead equilibrium between bone and other body compartments is unclear.

As typified by the results of the second National Health Assessment and Nutritional Evaluation Survey (NHANES II) (Mahaffey et al., 1979), children at 2-3 years of age show a small peak in blood lead. The question arises whether this peak indicates an intrinsic biological factor, such as increased absorption or retention when compared with older children, or whether this age group is exposed to lead in some special way. Several studies are relevant to the question. Zielhuis et al. (1978) reported data for blood lead levels in 48 hospitalized Dutch children, who ranged in age from 2 months to 6 years. Children up to 3 years old had a mean blood lead level of 11.9 μg/dl versus a level of 15.5 in children aged 4-6 years. A significant positive relationship between child age and blood lead was calculated ($r = 0.44$, $p < 0.05$). In the Danish survey by Nygaard et al. (1977), a subset of 126 children representing various geographical areas and age groups yielded the following blood lead values by mean age group: children ($N = 8$) with a mean age of 1.8 years had a mean blood lead level of 4.3 μg/dl; those with a mean age of 3.7-3.9 years had values ranging from 5.6 to 8.3 μg/dl; and children 4.6-4.8 years of age had a range of 9.2 to 10 μg/dl. These authors note that the youngest group was kept at a nursery, whereas the older kindergarten children had more interaction with the outside environment. Sartor and Rondia (1981) surveyed two population groups in Belgium, one of which consisted of groups of children aged 1-4, 5-8, and 9-14 years. Children under the age of 1 year had a mean blood lead level of 10.7 μg/dl. The 1- to 4-year and 5- to 8-year age groups were comparable, 13.9 and 13.7 μg/dl, respectively, while those 9-14 years old had a blood lead level of 17.2 μg/dl. All of the children in this study were hospital patients. While these European studies suggest that any significant restriction of children in terms of environmental interaction, e.g., in hospitals or nurseries, is associated with an apparently different age-blood lead relationship than the U.S. NHANES II subjects, whether European children in the 2- to 3-year age group show a similar peak remains to be demonstrated. The issue merits further study.

The normal mouthing activity of young children, as well as the actual ingestion of nonfood items (i.e., pica), is a major concern in pediatric lead exposure, particularly in urban areas with deteriorating housing stock and high automobile density and in nonurban areas contiguous to lead-production facilities. The magnitude of such potential exposures is discussed in Chapter 7, and an integrated assessment of impact on human intake appears in Chapter 13. Such intake is intensified for children with pica and would include paint, dust, and dirt.

Drill et al. (1979), using data from Day et al. (1975) and Lepow et al. (1974), have attempted to quantify the daily intake of soil/dust in young children from such mouthing activities as thumb sucking and finger licking. A total of 100 mg/day was obtained for children 2-3 years old, but the amount of lead in this ingested quantity varied considerably from site to site. In the report, a GI absorption rate of 30 percent was estimated for lead in soil and dust. Of relevance to this estimate are the animal data discussed in the next section, which show that lead of variable chemical forms in soil or dust is as available for absorption as lead in food. The *in vitro* studies relating lead solubility in street dusts with acidity clearly demonstrate that the acidity of the human stomach is adequate to extensively solubilize lead assimilated from soil and dust. To the extent that ingestion of such material by children occurs other than at mealtime, the fasting factor in enhancing lead absorption from the human GI tract (*vide supra*) must also be considered. Hence, a factor of 30 percent for lead absorption from dusts and soils is not an unreasonable value.

A National Academy of Sciences (NAS) report on lead poisoning in children has estimated that paint chip ingestion by children with pica occurs with considerable frequency (National Academy of Sciences, 1976). In the case of paint chips, Drill et al. (1979) estimated an absorption rate as high as 17 percent. This value may be compared with the animal data in Section 10.2.2.2, which indicate that lead in old paint films can undergo significant absorption in animals.

10.2.2.2 *Animal Studies*. Lead absorption via the gut of various adult experimental animal species appears to resemble that for the adult human, on the order of 1-15 percent in most cases. Kostial and her coworkers (Kostial and Kello, 1979; Kostial et al., 1978, 1971) reported a value of 1 percent or less in adult rats maintained on commercial rat chow. These studies were carried out using radioisotopic tracers. Similarly, Barltrop and Meek (1975) reported an absorption rate of 4 percent in control diets, while Aungst et al. (1981) found the value to range from 0.9 to 6.9 percent, depending on the level of lead given in the diet. In these rat studies, lead was ingested with food. Quarterman and Morrison (1978) administered ^{203}Pb label in small amounts of food to adult rats and found an uptake rate of approximately 2 percent at 4 months of age. Pounds et al. (1978) obtained a value of 26.4 percent with four adult Rhesus monkeys given ^{210}Pb by gastric intubation. The higher rate, relative to the rat, may reflect various states of fasting at time of intubation or differences in dietary composition (*vide infra*), two factors that affect rates of absorption.

As seen above with human subjects, fasting appears to enhance the rate of lead uptake in experimental animals. Garber and Wei (1974) found that fasting markedly enhanced gut uptake of lead in rats. Forbes and Reina (1972) found that lead dosing by gastric intubation of rats yielded an absorption rate of 16 percent, which is higher than other data for the rat indicate. Intubation was likely done when little food was in the gut. The data of Pounds et al.

(1978), as described above, may also suggest a problem with administering lead by gastric intubation or mixed with water as opposed to food.

The bioavailability of lead in the GI tract of experimental animals has been the subject of a number of reports. The designs of these studies differ in regard to how "bioavailability" is defined. In some cases, the dietary matrix was kept constant, or nearly so, while the chemical or physical form of the lead was varied. By contrast, other data described the effect of changes in bioavailability as the basic diet matrix was changed. The latter case is complicated by the simultaneous operation of lead-nutrient interactive relationships (described in Section 10.5.2).

Allcroft (1950) observed comparable effects when calves were fed lead in the form of the phosphate, oxide, or basic carbonate ($PbCO_3 \cdot Pb(OH)_2$), or incorporated into wet or dry paint. By contrast, lead sulfide in the form of finely ground galena ore was less toxic. Criteria for relative toxicity included kidney and blood lead levels and survival rate over time.

In the rat, Barltrop and Meek (1975) carried out a comparative absorption study using lead in the form of the acetate as the reference substance. The carbonate and thallate were absorbed to the greatest extent, while absorption of the sulfide, chromate, napthenate, and octoate was 44-67 percent of the reference agent. Barltrop and Meek (1979) also studied the relationship of the size of lead particles (as the metal or as lead octoate or chromate in powdered paint films) to the amount of gut absorption in the rat; they found an inverse relationship between uptake and particle size for both forms.

Gage and Litchfield (1968, 1969) found that lead napthenate and chromate can undergo considerable absorption from the rat gut when incorporated into dried paint films, although less than when given with other vehicles. Ku et al. (1978) found that lead in the form of the acetate or as a phospholipid complex was equally absorbed from the GI tract of both adult and young rats at a level of 300 ppm. Uptake was assessed by weight change, tissue levels of lead, and urinary aminolevulinic acid (ALA) levels.

In a study relevant to the problem of lead bioavailability in soils and dusts, particularly in exposed children, Dacre and Ter Haar (1977) compared the effects of lead as acetate with lead contained in roadside soil and in house paint soil, at a level of approximately 50 ppm, in commercial rat chow. Uptake of lead was indexed by weight change, tissue lead content, and inhibition of aminolevulinic acid dehydrase (ALA-D) activity. None of these parameters differed significantly across the three groups, suggesting that neither the geochemical matrix in the soils nor the various chemical forms (basic carbonate in paint soil, and the oxide, carbonate, and basic carbonate in roadside soil) affect lead uptake.

These data are consistent with the behavior of lead in dusts upon acid extraction as reported by Day et al. (1979), Harrison (1979), and Duggan and Williams (1977). In the Day et al. study, street dust samples from England and New Zealand were extracted with hydrochloric acid (HCl) over the pH range of 0-5. At an acidity that may be equalled by gastric secretions, i.e., pH of 1, approximately 90 percent of the dust lead was solubilized. Harrison (1979) noted that at this same acidity, up to 77 percent of Lancaster, England, street-dust lead was soluble, while an average 60 percent solubility was seen in London dust samples (Duggan and Williams, 1977). Because gastric solubilization must occur for lead in these media to be absorbed, the above data are useful in determining relative risk.

Kostial and Kello (1979) compared the absorption of ^{203}Pb from the gut of rats maintained on commercial rat chow versus rats fed such "human" diets as baby foods, porcine liver, bread, and cow's milk. Absorption in the latter cases varied from 3 to 20 percent, compared with <1.0 percent with rat chow. This range of uptake for the nonchow diet compares closely with that reported for human subjects (vide supra). Similarly, Jugo et al. (1975a) observed that rats maintained on fruit diets had an absorption rate of 18-20 percent. The generally observed lower absorption of lead in the adult rat compared to the adult human appears, then, less reflective of a species difference than of a dietary difference.

A number of studies have documented that the developing animal absorbs a relatively greater fraction of ingested lead than does the adult, thus supporting studies showing this age dependency in humans. For example, the adult rat absorbs approximately 1 percent lead or less via diet versus a corresponding value 40-50 times greater in the rat pup (Kostial et al., 1971, 1978; Forbes and Reina, 1972). In the rat, this difference persists through weaning (Forbes and Reina, 1972), at which point uptake resembles that of adults. Part of this difference can be ascribed to the nature of the diet (mother's milk versus regular diet), although the extent of absorption enhancement with milk versus rat chow in the adult rat found by Kello and Kostial (1973) fell short of what is seen in the neonate. An undeveloped, less selective intestinal barrier may also exist in the rat neonate. In nonhuman primates, Munro et al. (1975) observed that infant monkeys absorbed 65-85 percent via the gut versus 4 percent in adults. Similarly, Pounds et al. (1978) noted that juvenile rhesus monkeys absorbed approximately 50 percent more lead than adults.

The question of the relationship of level of lead intake through the GI tract and rate of lead absorption was addressed by Aungst et al. (1981), who exposed adult and suckling rats to doses of lead by intubation over the range 1-100 mg/kg or by variable concentrations in drinking water. With both age groups and both forms of oral exposure, lead absorption as a percentage of dose decreased, suggesting a saturation phenomenon for lead transport across the gut wall.

Similar data were obtained by Bushnell and DeLuca (1983) for weanling rats given ^{203}Pb by intubation along with carrier doses of 1, 10, 100, or 1000 ppm in diet. The GI absorption rate was observed to decrease significantly between 10 and 100 ppm carrier lead. Using isolated duodenal loop preparations, Conrad and Barton (1978) reported that lead uptake across the gut wall was constant from 0.001 to 10 ppm lead, but fell off to 40 percent of the 10-ppm level at the 100-ppm dosing.

The above concentration dependency is consistent with a saturable, active transport process for lead in the mammalian gut, based on the kinetic data of Aungst and Fung (1981). Mykkänen and Wasserman (1981) also noted that lead uptake by chick intestine occurs in two kinetic phases; a rapid uptake is followed by a rate-limiting slow transfer of lead. These kinetic observations agree with an increasingly retarded active transport process as lead content increases in the gut; i.e., lead affects its own transport, manifested as an increasingly lower absorption rate at higher lead intake.

Of interest here is the comparison of the kinetic behavior of blood lead as a function of oral versus parenteral dosing. With single intravenous injections of 0.5, 1, 5, 10, and 15 mg Pb/kg lead in the rat, Aungst et al. (1981) did not observe any dose dependency of the kinetic rate coefficients governing lead in blood. Integrated exposure, i.e., area under the blood lead curves, increased linearly with dose. On the other hand, injection of lead into rabbits at levels of 5, 10, 25, 50, and 500 µg/kg, by single daily injections for 6 days, resulted in clear curvilinearity to the dose-blood lead curve (Prpić-Majić et al., 1973). The differences in these two reports probably reflect dosing regimen differences: Aungst et al. (1981) used a higher dosing level as single exposures.

The implication of these experimental findings for human oral lead exposure is not clear. As noted earlier, lead intake orally by human subjects up to 400 µg is associated with a rather fixed absorption rate. Direct extrapolation of the animal data described above indicates that humans would have to ingest 20 to 200 mg lead per day (assuming a 2-kg diet/day at lead contents of 10 or 100 ppm) to have a lowered absorption rate. This value is up to 4500-fold above the upper oral intake guideline for lead (National Academy of Sciences, 1980).

10.2.3 Percutaneous Absorption of Lead

Absorption of inorganic lead compounds through the skin appears to be considerably less significant than uptake through the respiratory and GI routes. This observation contrasts with observations for lead alkyls and other organic derivatives (see Section 10.7). Rastogi and Clausen (1976) found that cutaneous or subcutaneous administration of lead napthenate in rat skin was associated with higher lead tissue levels and more severe toxic effects than was the case for lead acetate. Laug and Kunze (1948) applied lead as the acetate, orthoarsenate, oleate, and ethyl lead to rat skin and determined that the greatest levels of kidney lead were associated with the alkyl contact.

Moore et al. (1980) studied the percutaneous absorption of ^{203}Pb-labeled lead acetate in cosmetic preparations using eight adult volunteers. Applied in wet or dry forms, absorption was indexed by blood, urine, and whole body counting. Absorption rates ranged from 0 to 0.3

percent, with the highest values obtained when the application sites were scratched. These researchers estimated that the normal use of such preparations would result in an absorption of approximately 0.06 percent.

10.2.4 Transplacental Transfer of Lead

Lead uptake by the human and animal fetus occurs readily, based on such indices as fetal tissue lead measurements and, in the human, cord blood lead levels. Barltrop (1969) and Horiuchi et al. (1959) demonstrated by fetal tissue analysis that placental transfer in the human occurs by the 12th week of gestation, with fetal lead uptake increasing throughout development. The highest lead levels occur in bone, kidney, and liver, followed by blood, brain, and heart. Cord blood contains significant amounts of lead, which generally correlate with maternal blood values and are slightly but significantly lower in concentration than the mother's (Scanlon, 1971; Harris and Holley, 1972; Gershanik et al., 1974; Buchet et al., 1978; Alexander and Delves, 1981; Rabinowitz and Needleman, 1982).

A cross-sectional study of maternal blood lead levels carried out by Alexander and Delves (1981) showed that a significant decrease in maternal blood lead occurs throughout pregnancy, a decrease greater than the dilution effect of the concurrent increase in plasma volume. Hence, during pregnancy there is either an increasing deposition of lead in placental or fetal tissue or an increased loss of body lead via other routes. Increasing absorption by the fetus during gestation, as demonstrated by Barltrop (1969), implies that the former explanation is likely. Hunter (1978) found that summer-born children showed a trend toward higher blood lead levels than those born in the spring, suggesting increased fetal uptake in the summer resulting from increases in circulating maternal lead. This observation was confirmed in the report of Rabinowitz and Needleman (1982). Ryu et al. (1978) and Singh et al. (1978) both reported that infants born to women having a history of lead exposure had significantly elevated blood lead values at birth.

10.3 DISTRIBUTION OF LEAD IN HUMANS AND ANIMALS

A quantitative understanding of the sequence of changes in lead levels in various body pools and tissues is essential in interpreting measured lead levels with respect to past exposure as well as present and future risks of toxicity. This section discusses the distribution kinetics of lead in various portions of the body (blood, soft tissues, calcified tissues, and the "chelatable" or toxicologically active body burden) as a function of such parameters as exposure history and age.

A given quantity of lead taken up from the GI tract or the respiratory tract into the bloodstream is initially distributed according to the rate of delivery by blood to the various organs and systems. Lead is then redistributed to organs and systems in proportion to their respective affinities for the element. With consistent exposure for an extended period, a near steady state of intercompartmental distribution is achieved.

Fluctuations in the near steady state will occur whenever short-term lead exposures are superimposed on a long-term uptake pattern. Furthermore, the steady-state description is imperfect because, on a very short (hourly) time scale, intake is not constant. Lead intake with meals and changes in ambient air lead (outside to inside and vice versa) cause quick changes in exposure levels that may be viewed as short-term alterations in the small, labile lead pool. Metabolic stress could remobilize and redistribute body stores, although documentation of the extent to which this happens is very limited (Chisolm and Harrison, 1956).

10.3.1 Lead in Blood

Viewed from different time scales, lead in whole blood may be seen as residing in several distinct, interconnected pools. More than 99 percent of blood lead is associated with the erythrocytes (DeSilva, 1981; Everson and Patterson, 1980; Manton and Cook, 1979) under typical conditions, but it is the very small fraction of lead transported in plasma and extracellular fluid that provides lead to the various body organs (Baloh, 1974).

Although the toxicity of lead to the erythrocyte (Raghavan et al., 1981) is mainly associated with membrane lead content, most of the erythrocyte lead is bound within the cell. Within erythrocytes from nonexposed subjects, lead is primarily bound to hemoglobin, in particular HbA_2, which binds approximately 50 percent of cell lead while constituting only 1-2 percent of total hemoglobin (Bruenger et al., 1973). A further 5 percent is bound to a 10,000-dalton molecular-weight fraction, about 20 percent to a much heavier molecule, and about 25 percent is considered "free" or bound to lower-weight molecules (Ong and Lee, 1980a; Raghavan and Gonick, 1977). Raghavan et al. (1980) have observed that, among workers exposed to lead, those who develop signs of toxicity at relatively low blood lead levels seem to have a diminished binding of intracellular lead with the 10,000-dalton fraction. This reduction in binding suggests an impaired biosynthesis of a protective species. According to Ong and Lee (1980b), fetal hemoglobin has a higher affinity for lead than adult hemoglobin.

Whole blood lead in daily equilibrium with other compartments was found to have a mean life of 35 days (25-day half-life) and a total lead content of 1.9 mg, based on studies with a small number of subjects (Rabinowitz et al., 1976). Chamberlain et al. (1978) established a similar half-life for ^{203}Pb in blood when volunteers were given the label by ingestion, inhalation, or injection. The lead inhalation studies in adults described by Griffin et al.

(1975) permit calculation of half-lives of 28 and 26 days for inhalation of 10.4 and 3.1 μg Pb/m^3, respectively. These estimates of biological half-life, based as they are on isotopic study, do not reflect the impact of mobile body burden on half-life. The higher the mobilizable lead burden, the greater will be the length of the half-life, as clearly seen in the report of O'Flaherty et al. (1982), where half-life in lead workers was a function of cumulative occupational exposure.

Alterations in blood lead levels in response to abrupt changes in exposure apparently occur over somewhat different periods, depending on whether the direction of change is greater or smaller. With increased lead intake, blood lead level achieves a new value in approximately 60 days (Griffin et al., 1975; Tola et al., 1973). A decrease may involve a longer period of time, depending on the magnitude of the past higher exposure (O'Flaherty et al., 1982; Rabinowitz et al. 1977; Gross, 1981).

In adulthood, the human's blood lead level appears to increase moderately. Awad et al. (1981) reported an increase of 1 μg for each 14 years of age. However, in the NHANES II survey (see Chapter 11), white adults showed increasing blood lead until 35-44 years of age, followed by a decrease. By contrast, blacks showed increasing blood lead after 44. In the case of reduced exposure, particularly occupational exposure, the time for re-establishing near steady state depended more upon the extent of lead resorption from bone and the total quantity deposited, either of which can extend the "washout" interval.

Lead levels in newborn children are similar to but somewhat lower than those of their mothers: 8.3 versus 10.4 μg/dl (Buchet et al., 1978) and 11.0 versus 12.4 μg/dl (Alexander and Delves, 1981). Maternal blood lead levels decrease throughout pregnancy, the decrease being greater than the expected dilution via the concurrent increase in plasma volume (Alexander and Delves, 1981). This decrease in maternal blood lead levels suggests increased fetal uptake during gestation (Barltrop, 1969). Increased tissue retention of lead by the child may also be a factor.

Levels of lead in blood are sex related; adult women invariably show lower levels than adult males (e.g., Mahaffey et al., 1979). Of interest in this regard is the study of Stuik (1974) showing lower blood lead response in women than in men for an equivalent level of lead intake.

The small but biologically significant lead pool in blood plasma has proven technically difficult to measure, and reliable values have become available only recently (see Chapter 9). Chamberlain et al. (1978) found that injected ^{203}Pb was removed from plasma (and, by inference, from extracellular fluid) with a half-life of less than 1 hr. These data support the observation of DeSilva (1981) that lead is rapidly cleared from plasma. Ong and Lee (1980a), in their _in vitro_ studies, found that ^{203}Pb is virtually all bound to albumin and that only trace amounts are bound to high-weight globulins. To state which binding form constitutes an "active" fraction for movement to tissues is not possible.

Although Rosen et al. (1974) reported that plasma lead did not vary across a range of whole blood levels, the findings of Everson and Patterson (1980), DeSilva (1981), and Cavalleri et al. (1978) indicate that there is an equilibrium between red blood cells (RBCs) and plasma, such that levels in plasma rise with levels in whole blood. This observation is consistent with the data of Clarkson and Kench (1958), who found that lead in the RBC is relatively labile to exchange and a logical prerequisite for a dose-effect relationship in various organs. Ong and Lee (1980c), furthermore, found that plasma calcium is capable of displacing RBC membrane lead, suggesting that plasma calcium is a factor in the cell-plasma lead equilibrium.

Several studies concerning the relative distribution of lead between erythrocytes and plasma or serum indicate that the relative percentage of blood lead in plasma versus erythrocytes is relatively constant up to a blood lead concentration of about 50-60 µg/dl, but becomes increasingly greater above this level, i.e., the overall blood lead/plasma lead relationship is curvilinear upward.

DeSilva (1981) found that the relative fraction of plasma lead versus erythrocytes in 105 Australian lead workers increased at ~60 µg/dl. Similarly, Manton and Malloy (1983) observed that a subject having lead intoxication had serum lead values ranging from 1.6 to 0.3 percent as blood concentration changed from 116 to 31 µg/dl. More recently, Manton and Cook (1984) demonstrated a curvilinear relationship between serum and whole blood lead levels. As depicted in Figure 10-2, the curve indicates that there is a linear segment up to ~50 µg/dl, followed by rather steep increases in relative serum lead content at higher levels.

Measurement of lead in plasma by these investigators was carefully carried out, and the Manton reports involved the definitive lead analysis technique of isotope-dilution mass spectrometry (IDMS, see Chapter 9). Given the increased erythrocyte fragility with increasing blood lead content (see Section 12.3), slight hemolysis during sampling might contaminate plasma or serum with high erythrocyte lead and complicate such analyses; however, the reports did not indicate that hemolysis was considered a problem.

The biological basis for higher levels of plasma versus whole blood lead with increasing blood lead burden may be related to marked changes in the binding capacity of the erythrocyte at high lead content. These changes may result from alterations in binding sites or in the efficiency of lead movement from membrane to erythrocyte interior. Fukumoto et al. (1983) have demonstrated changes (in the form of a decrease) in lead-worker erythrocyte-membrane proteins that may have a role in lead transport. Perhaps more important are the long-known effects of lead exposure on erythrocyte morphology and destruction rate (see Section 12.3).

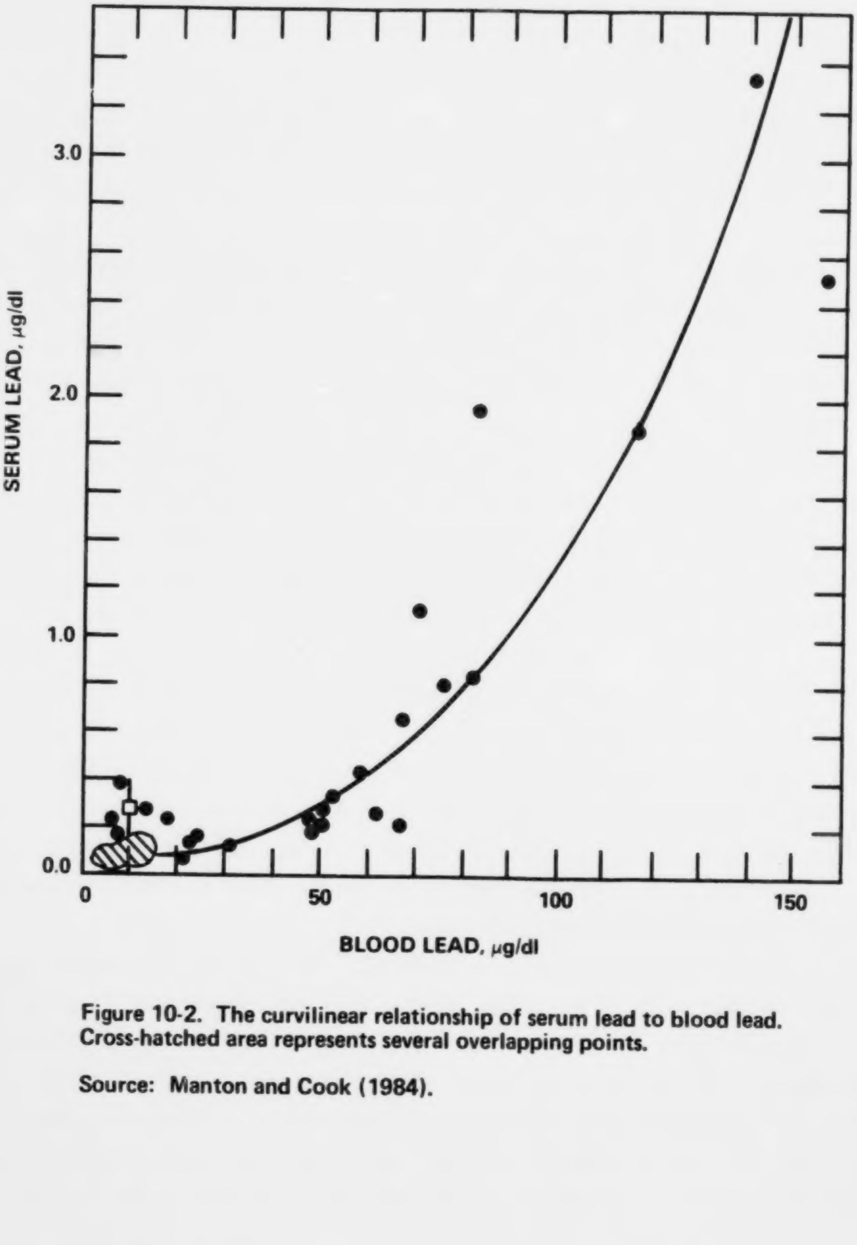


Figure 10-2. The curvilinear relationship of serum lead to blood lead. Cross-hatched area represents several overlapping points.

Source: Manton and Cook (1984).

Changes in cell morphology with increasing blood lead may alter accessibility to binding sites or the relative stability of these sites. Increased cell destruction may increase protein-bound cell lead in plasma, which is only slowly transferred back to cell membrane.

In vitro data concerning the concentration dependency of lead partitioning between erythrocytes and plasma are of interest. Keep in mind, however, that such *in vitro* data have employed normal erythrocytes. Clarkson and Kench (1958) showed that the relative partitioning between normal erythrocytes and plasma is relatively constant up to the highest level tested, equivalent to 100 μg Pb/dl. In the related study of Kochen and Greener (1973), tracer plus carrier lead was added to blood of varying hematocrit up to a maximum addition of 1000 μg/dl. At a normal hematocrit and a higher value (0.65), the percent uptake of lead label by the cells diminished at around 100 μg/dl, consistent with the Clarkson and Kench (1958) data. Onset of curvilinearity at a lower blood lead level *in vivo* in lead-exposed subjects below the *in vitro* value of ∿100 μg/dl probably reflects in part altered cell morphology and stability (DeSilva, 1981; Manton and Malloy, 1983; Manton and Cook, 1984).

The curvilinear relationship of plasma to whole blood lead may well be a factor in Chamberlain's (1983) observation that the relative rate of urinary excretion of lead in human adults increases with blood lead content, as determined from various published reports providing both blood and urinary lead data (see Section 10.4). It may also figure in the apparently better proportionality of tissue lead burdens to dose than blood lead (*vide infra*) and, equally important, the curvilinear relationship of chelatable lead to blood lead. That is, at increasing blood lead, the higher relative rate of plasma lead movement to soft tissues and bone is greater than would be anticipated from simple inspection of blood lead content, the latter rising at a slower rate relative to the increase in plasma lead.

10.3.2 Lead Levels in Tissues

Of necessity, various relationships of tissue lead to exposure and toxicity in humans generally must be obtained from autopsy samples, although in some studies biopsy data have been described. The inherent question then is whether such samples adequately represent the behavior of lead in the living population, particularly in cases where death was preceded by prolonged illness or disease states. Also, victims of fatal accidents are not well characterized as to exposure status and are usually described as having no "known" lead exposure. Finally, these studies are necessarily cross-sectional in design, and, in the case of body accumulation of lead, different age groups are assumed to have been similarly exposed. Some important aspects of the available data include the distribution of lead between soft and calcifying tissue, the effect of age and development on lead content of soft and mineral tissue, and the relationship between total and "active" lead burdens in the body.

10.3.2.1 Soft Tissues. In humans over age 20 most soft tissues do not show age-related changes in lead levels, in contrast to the case with bone (Barry and Mossman, 1970; Barry, 1975, 1981; Schroeder and Tipton, 1968; Butt et al., 1964). Kidney cortex also shows increases in lead with age that may be associated with formation of lead nuclear inclusion bodies (Indraprasit et al., 1974). Based on these rates of accumulation, the total body burden may be divided into pools that behave differently. The largest and kinetically slowest pool is the skeleton, which accumulates lead with age. The much more labile lead pool is in soft tissue.

Soft-tissue lead levels generally stabilize in early adult life and show a turnover rate similar to that for blood. This turnover is sufficient to prevent accumulation except in the renal cortex, which may reflect formation of lead-containing nuclear inclusion bodies (Cramer et al., 1974; Indraprasit et al., 1974). The data of Gross et al. (1975) and Barry (1975) indicate that aortic levels rise with age, although this rise may only reflect entrapment of lead in atherosclerotic deposits. Biliary and pancreatic secretions, while presumably reflecting some of the organ levels, have tracer lead concentrations distinct from either blood or bone pools (Rabinowitz et al., 1973).

For levels of lead in soft tissue, the reports of Barry (1975, 1981), Gross et al. (1975), and Horiuchi et al. (1959) indicate that soft-tissue content generally is below 0.5 µg/g wet weight, with higher values for aorta and kidney cortex. The higher values in aorta may or may not reflect lead in plaque deposits, while higher kidney levels may be associated with the presence of lead-accumulating tubular cell nuclear inclusions. The relatively constant lead concentration in lung tissue across age groups suggests no accumulation of respired lead and is consistent with data for deposition and absorption (see Section 10.2.1). Brain tissue was generally under 0.2 ppm wet weight and appeared to show no change with increasing age. Since these data were collected by cross-sectional study, age-related changes in the low levels of lead in brain would have been difficult to discern. Barry (1975) found that tissues in a small group of samples from subjects with known or suspected occupational exposure showed higher lead levels in aorta, liver, brain, skin, pancreas, and prostate.

Analysis of lead levels in whole brain is less illuminating than regional analysis to the issue of sensitivity of certain regions within the organ to toxic effects of lead. The distribution of lead across brain regions has been reported by various laboratories. The relevant data for humans and animals are set forth in Table 10-2. The data of Grandjean (1978) and Niklowitz and Mandybur (1975) for human adults, and those of Okazaki et al. (1963) for autopsy samples from young children who died of lead poisoning, are consistent in showing that lead is selectively accumulated in the hippocampus. The correlation of lead level with potassium level suggests that uptake of lead is greater in cellulated areas. The involvement of

TABLE 10-2. DISTRIBUTION OF LEAD IN BRAIN REGIONS OF HUMANS AND ANIMALS

Subjects	Exposure status	Relative distribution	Reference
Humans			
Adult males	"Unexposed"	Hippocampus ≅ amygdala > medulla oblongata > half brain > optic tract ≅ corpus callosum. Pb correlated with potassium.	Grandjean (1978)
Children	Fatal lead poisoning	Hippocampus > frontal cortex >> occipital white matter, pons	Okazaki et al. (1963)
Child, 2 yr old	Fatal lead poisoning	Cortical gray matter > basal ganglia > cortical white matter	Klein et al. (1970)
Adults	3 subjects "unexposed"; 1 subject with lead poisoning as child	Hippocampus > cerebellum ≅ temporal lobes > frontal cortex in 3 unexposed subjects; temporal lobes > frontal cortex > hippocampus > cerebellum in case with prior exposure	Niklowitz and Mandybur (1975)
Animals			
Adult rats	"Unexposed"	Hippocampus > amygdala >> whole brain	Danscher et al. (1975)
Adult rats	"Unexposed"	Hippocampus had 50% of brain lead with a 4:1 ratio of hippocampus to whole brain concentrations	Fjerdingstad et al. (1974)
Neonatal rats	Controls and daily i.p. injection, 5.0 or 7.5 mg/kg	In both treated and control animals cerebellum > cerebral cortex > brainstem + hippocampus	Klein and Koch (1981)
Young dogs	Controls and dietary exposure, 100 ppm; 12 weeks of exposure	Controls: cerebellum ≅ medulla > caudate > occipital gray > frontal gray Exposed: occipital gray > frontal gray ≅ caudate > occipital white ≅ thalamus > medulla > cerebellum	Stowe et al. (1973)

the cerebellum in lead encephalopathy in children (see Section 12.4) and in adult intoxication from occupational exposure indicates that the sensitivity of various brain regions to lead as well as their relative uptake characteristics are factors in lead neuropathology.

In adult rats, selective uptake of lead is shown by the hippocampus (Fjerdingstad et al., 1974; Danscher et al., 1975) and the amygdala (Danscher et al., 1975). By contrast, lead-exposed neonate rats show greatest uptake of lead into cerebellum, followed by cerebral cortex, then brainstem plus hippocampus. Hence, there is a developmental difference in lead distribution in the rat with or without increased lead exposure (Klein and Koch, 1981).

In studies of young dogs, "unexposed" animals showed highest levels in the cerebellum. Increased lead exposure was associated with selective uptake into gray matter, while cerebellar levels were relatively low. Unlike the young rat, then, the distribution of lead in brain regions of dogs appears dose-dependent (Stowe et al., 1973).

The relationship of lead distribution to various tissues with changes in lead exposure has not been well researched. Available information does suggest that the nature of lead exposure in experimental animals influences the relationship of tissue lead level to both blood lead level and level of intake. Long-term oral exposure of experimental animals at relatively moderate dosing would appear to result in tissue values that show more proportionality to dose than do blood lead values, although tissue versus blood lead relationships still appear to be curvilinear. Such is the case with dogs exposed to dietary lead for 2 years (Azar et al., 1973) and rats exposed _in utero_ and postnatally up to 9 months of age (Grant et al., 1980).

By contrast, short-term exposure at various dosing levels yields highly variable data (see Section 12.4.3.5 and Table 12-8). Bull et al. (1979) have reported brain and blood lead data for dam-exposed suckling rats that show marked deviation from linear response to dose when lead was administered in drinking water at 0.0005 to 0.02 percent lead. Over this 40-fold oral dosing range, brain lead levels increased only approximately threefold at 21 days of age. Whether this low absorption of lead by brain reflects tissue distribution curvilinearity in the pups or reflects a function of nonlinear milk lead versus maternal dosing relationships cannot be determined. Collins et al. (1982) reported that rats orally exposed to lead from 3 days of age for 4-8 weeks showed a two- to threefold increase in brain regions when the dosing level was increased to 1.0 mg/kg from 0.1 mg/kg. Blood lead at these two dosing levels showed a concentration ratio of ~2.5, indicating that both brain tissue and blood showed similar nonlinear response over this 10-fold change in oral exposure.

Barry (1975, 1981) compared lead levels in soft tissues of children and adults. Tissue lead of infants under 1 year old was generally lower than in older children, while children aged 1-16 years had values that were comparable to those for adult women. In Barry's (1981) study, the absolute concentration of lead in brain cortex or the ratios of brain cortex to blood lead levels did not appear to be different in infants or older children compared to adults. Such direct comparisons do not account for relative tissue mass changes with age, but this factor is comparatively less with soft tissue than with the skeletal system (see Section 10.4).

Subcellular distribution of lead in soft tissue is not uniform, with high amounts of lead being sequestered in the mitochondria and nucleus. Cramer et al. (1974) studied renal biopsy tissue in lead workers having exposures of variable duration. They observed lead-binding nuclear inclusion bodies in the renal proximal tubules of subjects having short exposure, with all showing mitochondrial changes. A considerable body of animal data (see Section 10.3.5) documents the selective uptake of lead into these organelles. Pounds et al. (1982) describe these organellar pools in kinetic terms as having comparatively short half-lives in cultured rat hepatocytes, while McLachlin et al. (1980) found that rat kidney epithelial cells form lead-sequestering nuclear inclusions within 24 hr.

10.3.2.2 Mineralizing Tissue. Biopsy and autopsy data have shown that lead becomes localized and accumulates in human calcified tissues, i.e., bones and teeth. The accumulation begins with fetal development (Barltrop, 1969; Horiuchi et al., 1959).

Total lead content in bone may exceed 200 mg in men aged 60 to 70 years, but in women the accumulation is somewhat lower. Various investigators (Barry, 1975; Horiguchi and Utsunomiya, 1973; Schroeder and Tipton, 1968; Horiuchi et al., 1959) have documented that approximately 95 percent of total body lead is lodged in bone. These reports not only establish the affinity of bone for lead, but also provide evidence that lead increases in bone until 50-60 years of age, the later fall-off reflecting some combination of diet and mineral metabolism changes. Tracer data show accumulation in both trabecular and compact bone (Rabinowitz et al., 1976).

In adults, bone lead is the most inert pool as well as the largest, and accumulation can serve to maintain elevated blood lead levels years after past, particularly occupational, exposure has ended. This fact accounts for the observation that duration of exposure correlates with the rate of reduction of blood lead after termination of exposure (O'Flaherty et al., 1982). The proportion of body lead lodged in bone is reported to be lower in children than in adults, although concentrations of lead in bone increase more rapidly than in soft tissue during childhood (Barry, 1975, 1981). In 23 children, bone lead was 9 mg, or 73 percent of total body burden, versus 94 percent in adults. Expression of lead in bone in terms of concentration across age groups, however, does not accommodate the "dilution" factor, which is quite large for the skeletal system in children (see Section 10.4).

The isotope kinetic data of Rabinowitz et al. (1976) and Holtzman (1978) indicate biological half-lives of lead in bone on the order of several decades, although it appears that there are two bone compartments, one of which is a repository for relatively labile lead (Rabinowitz et al., 1977).

Tooth lead levels also increase with age at a rate proportional to exposure (Steenhout and Pourtois, 1981), and are also roughly proportional to blood lead levels in man (Winneke et al., 1981; Shapiro et al., 1978) and experimental animals (Kaplan et al., 1980). Dentine lead is perhaps the most responsive component of teeth to lead exposure because it is laid down from the time of eruption until the tooth is shed. Needleman and Shapiro (1974) have documented the usefulness of dentine lead as an indicator of the degree of subject exposure. Fremlin and Edmonds (1980), using alpha-particle excitation and microautoradiography, have shown dentine zones of lead enrichment related to abrupt changes in exposure. The rate of lead deposition in teeth appears to vary with the type of tooth. Deposition is highest in the central incisors and lowest in the molars, a difference that must be taken into account when using tooth lead data for exposure assessment, particularly for low levels of lead exposure (Mackie et al., 1977; Delves et al., 1982).

10.3.3 Chelatable Lead

Mobile lead in organs and systems is potentially more "active" toxicologically in terms of being available to sites of action. Hence, the presence of diffusible, mobilizable, or exchangeable lead may be a more significant predictor of imminent toxicity or recent exposure than total body or whole blood burdens. In reality, however, assays for mobile lead would be quite difficult.

In this regard, chelatable urinary lead has been shown to provide an index of this mobile portion of total body burden. Note that "chelatable" lead refers here to the use of calcium disodium ethylenediaminetetraacetic acid ($CaNa_2EDTA$) and body compartments accessible to this chelant. Based mainly on the relationship of chelatable lead to indices of heme biosynthesis impairment, chelation challenge is now viewed as the most useful probe of undue body burden in children and adults (U.S. Centers for Disease Control, 1978; World Health Organization, 1977; Chisolm and Barltrop, 1979; Chisolm et al., 1976; Saenger et al., 1982; Hansen et al., 1981). In adults, chelation challenge is the most reliable diagnostic test for assessment of lead nephropathy, particularly when exposure is remote in time (Emerson, 1963; Wedeen et al., 1979) or unrecognized (Batuman et al., 1981, 1983).

A quantitative description of inputs to the fraction of body lead that is chelatable from various body compartments is difficult to define fully, but it very likely includes a sizable, fairly mobile compartment within bone as well as within soft tissues. This assertion is based on several factors. First, the amount of lead mobilized by chelation is age-dependent in non-exposed adults (Araki, 1973; Araki and Ushio, 1982), while blood and soft-tissue lead levels are not (Barry, 1975). This difference indicates a lead pool labile to chelation but kinetically distinct from soft tissue. Second, studies of chelatable lead in animals (Hammond, 1971, 1973) suggest removal of some bone lead fraction, as does the response of explanted fetal rat bone lead to chelants (Rosen and Markowitz, 1980). Third, the tracer modeling estimates of Rabinowitz et al. (1977) suggest a mobile bone compartment, and fourth, there is a complex, nonlinear relationship of lead intake by air, food, and water (see Chapter 11) to blood lead, and an exponential relationship of chelatable lead to blood lead (Chisolm et al., 1976).

The logarithmic relationship of chelatable lead to blood lead in children (Chisolm et al., 1976) is consistent with the studies of Saenger et al. (1982), who reported that levels of mobilizable lead in "asymptomatic" children with moderate elevations in blood lead were quite similar in many cases to those values obtained in children with signs of overt toxicity. Hansen et al. (1981) reported that lead workers challenged with $CaNa_2EDTA$ showed 24-hr urine lead levels that in many cases exceeded the accepted limits even though blood lead was only moderately elevated in many of those workers. The action level corresponded, on the regression curve, to a blood lead value of 35 µg/dl.

Several reports provide insight into the behavior of labile lead pools in children treated with chelating agents over varying periods of time. Treatment regimens using $CaNa_2EDTA$ or $CaNa_2EDTA$ + BAL (British anti-Lewisite, or dimercaprol) for up to 5 days have been invariably associated with a "rebound" in blood lead, ascribed to a redistribution of lead among mobile lead compartments (Chisolm and Barltrop, 1979). Marcus (1982) reported that 41 children given oral D-penicillamine for 3 months showed a significant drop in blood lead by 2 weeks (mean initial value of 53.2 µg/dl), then a slight rise that was within measurement error with a peak at 4 weeks, and a fall at 6 weeks, followed by no further change at a blood lead level of 36 µg/dl. Hence, there was a near steady state at an elevated level for 10 of the 12 weeks with continued treatment. This observation could have indicated that re-exposure was occurring, with oral penicillamine and ingested lead leading to increased lead uptake, as seen by Jugo et al. (1975a). However, Marcus (1982) stated that an effort was made to limit further lead intake as much as possible. From these reports, a re-equilibration does appear to occur, varying in characteristics with type and duration of chelation. The rebound seen in short-term treatment with $CaNa_2EDTA$ or $CaNa_2EDTA$ + BAL, although attributed to soft tissue, could well include a shift of lead from a larger mobile bone compartment to soft tissues and blood. The apparent steady state between the blood lead pool and other compartments that is achieved in the face of plumburesis, induced by D-penicillamine (Marcus, 1982), suggests a rather sizable labile body pool which, in quantitative terms, would appear to exceed that of soft tissue alone.

Several studies of EDTA mobilization of lead in children (Saenger et al., 1982; Piomelli et al., 1984) indicate the relative merit of assessing chelatable lead burden in children otherwise characterized as having mild or moderate lead exposure as indicated by blood lead levels. Saenger et al. (1982) noted that significant percentages of children having mild or moderate lead exposure as commonly indexed were found after EDTA challenge to have levels of plumburesis that would qualify them for chelation therapy under U.S. Centers for Disease Control (CDC) guidelines.

In the most comprehensive evaluation of this issue to date (Piomelli et al., 1984), 210 children from four different urban lead-poisoning treatment centers were evaluated by EDTA provocation testing. The results showed that at a blood lead level of 30-39 μg/dl, 12 percent (6/52) of children exceed the ratio of 0.6 for μg Pb excreted per mg EDTA per 8 hr. This ratio was selected by the study clinicians as differentiating children with mobile lead burdens who require further evaluation and/or treatment. Thirty-eight percent of children with blood lead levels of 40-49 μg/dl exceeded the action ratio of 0.6.

As indicated in Section 10.3.1, one basis for the curvilinear relationship between chelatable lead and blood lead may be the curvilinear relationship of plasma lead to blood lead. The former increases at a faster rate with exposure increases than blood lead, permitting an increasingly greater rate of lead transfer to the chelatable lead compartment.

10.3.4 Mathematical Descriptions of Physiological Lead Kinetics

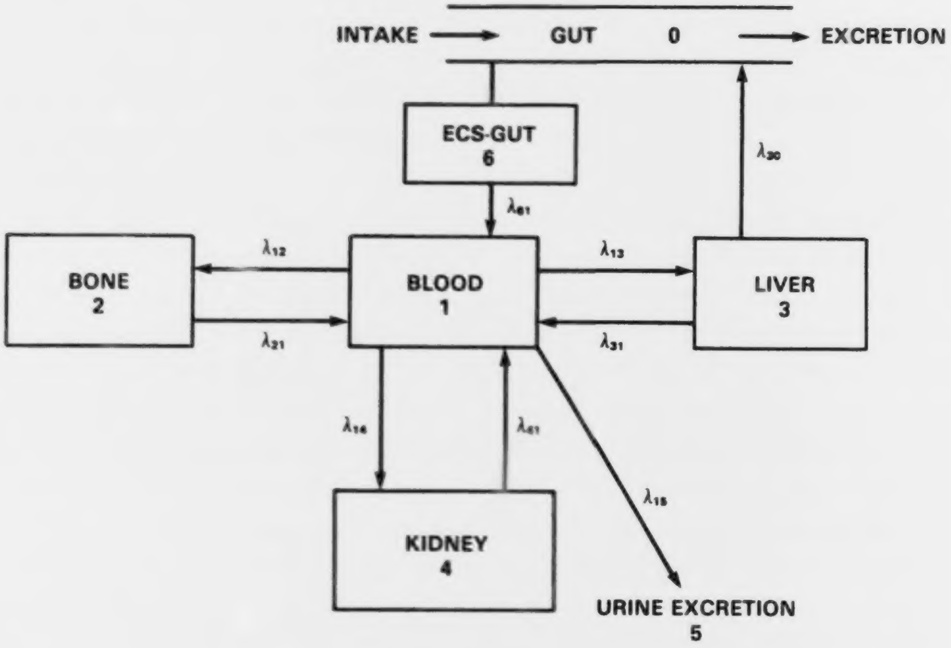
To account for observed kinetic data and make predictive statements, a variety of mathematical models have been suggested, including those describing "steady-state" conditions. Tracer experiments have suggested compartmental models of lead turnover based on a central blood pool (Holtzman, 1978; Rabinowitz et al., 1976; Batschelet et al., 1979). These experiments have hypothesized well-mixed, interconnected pools and have used coupled differential equations with linear exponential solutions to predict blood and tissue lead exchange rates. Were lead to be retained in these pools in accordance with a power-law distribution of residence times, rather than being uniform, a semi-Markov model would be more appropriate (Marcus, 1979).

In the model proposed by Rabinowitz et al. (1976), based on the use of stable lead isotope tracer in adult volunteers, lead biokinetics is envisioned in terms of three body compartments. These compartments, consisting of a central blood compartment as well as soft-tissue and bone compartments, differ as to biological half-lives or mean-lives (half life = mean-life x 0.693). Blood shows the shortest biological half-life, followed by soft tissue and then the bone compartment. Bone contains most of total body lead burden.

A more recent approach has been that of Kneip et al. (1983) for multi-organ compartmentalization of lead, based on data obtained with infant and juvenile baboons administered single and chronic lead doses orally. The model proposed for infant baboons is depicted in Figure 10-3. Figure 10-3 acknowledges differences in certain features of lead biokinetics that differ in the developing versus adult organism. One of these differences is the lead transfer rate from blood to bone. In addition, an extracellular space-gut (ECS-Gut) compartment is included in Figure 10-3. The emphasis is on lead intake through the gut, and a respiratory intake component is not included. In common with other attempts at modeling, the blood compartment in the approach of Kneip et al. (1983) is not further characterized kinetically, which is a limitation in view of the data base concerning such relationships as the curvilinear one between plasma and blood lead (see Section 10.3.2).

Most extant steady-state models are deficient because they are based on small numbers of subjects and neglect a dose dependency for some of the interpool transfer coefficients. In this case, a nonlinear dose-indicator response model would be more appropriate when considering changes in blood lead levels. For example, the relationship between blood lead and air lead (Hammond et al., 1981; Brunekreef, 1984) as well as that between diet (United Kingdom Central Directorate on Environmental Pollution, 1982) and tap drinking water (Sherlock et al., 1982) are all nonlinear in mathematical form. In addition, alterations in nutritional status or the onset of metabolic stresses can complicate steady-state relationships.

In a series of papers, Marcus (1985a,b,c,d) has discussed linear and nonlinear multicompartmental models of lead kinetics and has addressed in particular the relationship between plasma lead and blood lead and the relationship between blood lead and total lead intake. As shown in Figure 10-4, Marcus (1985d) differentiated four discrete pools within the blood compartment: diffusible lead in plasma, protein-bound lead in plasma, a "shallow" red blood cell pool (possibly the erythrocyte membrane), and a "deep" red blood cell pool (probably within the erythrocyte). This model was based on previously published data from a volunteer subject who ingested lead under controlled experimental conditions (DeSilva, 1981). Different versions of the model, all assuming steady-state conditions for lead in all tissues, were analyzed in terms of three possible mechanisms that might underlie nonlinear blood kinetics: site-limited lead uptake, saturated active absorption, and increased urinary elimination (Marcus, 1985c). The site-limited absorption model provided the best description of a nonlinear relationship between plasma lead and blood lead. Figure 10-5 shows the fit of the model to data from 103 subjects studied by DeSilva (1981). At relatively high blood lead levels, the fit appears quite satisfactory, but plasma lead is underestimated below 30 µg/dl blood lead (see solid line in Figure 10-5). Adding an intercept term of 0.25 (see broken line in Figure 10-5) improves the fit at low blood lead values. The need for an intercept term can



λ_{12} = 0.34 (INFANT) = 0.11 (JUVENILE)
λ_{21} = 1.73×10^{-3}
λ_{13} = 0.10
λ_{31} = 0.03
λ_{14} = 0.03
λ_{41} = 0.07
λ_{15} = 0.08
λ_{30} = 0.01
λ_{61} = 0.23

Figure 10-3. Schematic model of lead metabolism in infant baboons, with compartmental transfer coefficients.

Source: Kneip et al. (1983).

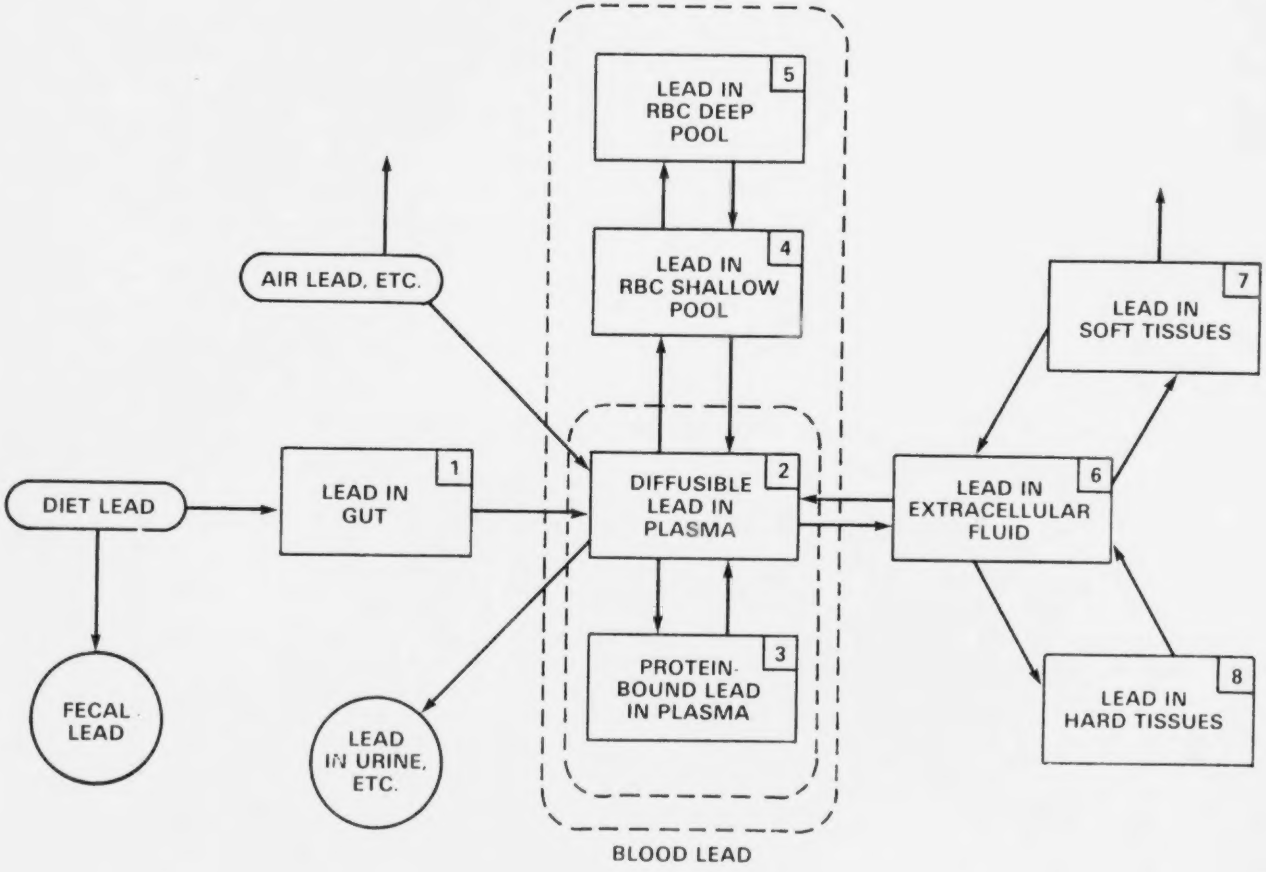


Figure 10-4. A compartmental model for lead biokinetics with multiple pools for blood lead.

Source: Marcus (1985d).

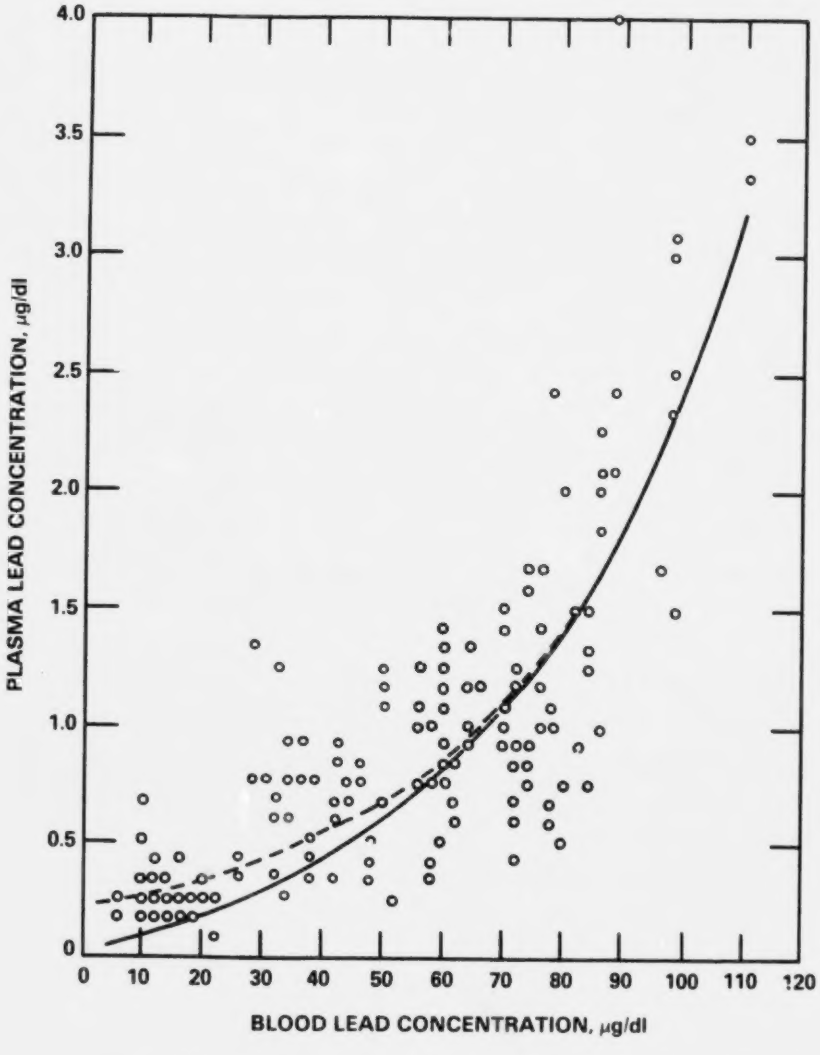


Figure 10-5. Fitting of nonlinear blood lead model to data of DeSilva (1981). Broken line incorporates an intercept term of 0.25; solid line does not incorporate intercept term.

Source: Marcus (1985c).

be attributed to possible analytic error due to contamination of the plasma samples or to transient fluctuations in plasma lead due to lead exposure just prior to sampling (Marcus, 1985c). In any event, curvilinearity is modest below 30 µg/dl. For individuals without occupational or other excessive exposure to lead (>30 µg/dl blood lead), it is not possible to distinguish linear and nonlinear kinetic models (Marcus, 1985c).

10.3.5 Animal Studies

The relevant questions to be asked of animal data are those that cannot be readily or fully satisfied by data from human subjects. What is the effect of exposure level on distribution within the body at specific time points? What is the relationship of age or developmental stage on the distribution of lead in organs and systems, particularly the nervous system? What are the relationships of physiological stress and nutritional status to the redistribution kinetics? Can the relationship of chelatable lead to such indicator lead pools as blood be defined better?

Administration of a single dose of lead to rats produces high initial lead concentrations in soft tissues, which then fall rapidly as the result of excretion and transfer to bone (Hammond, 1971), while the distribution of lead appears to be independent of the dose. Castellino and Aloj (1964) reported that single-dose exposure of rats to lead was associated with a fairly constant ratio of erythrocyte lead to plasma lead, a rapid distribution to tissues, and relatively higher uptake in liver, kidney, and particularly bone. Lead loss from organs and tissues follows first-order kinetics except from bone. The data of Morgan et al. (1977), Castellino and Aloj (1964), and Keller and Doherty (1980a) document that the skeletal system in rats and mice is the kinetically rate-limiting step in whole-body lead clearance.

Subcellular distribution studies involving either tissue fractionation after *in vivo* lead exposure or *in vitro* data document that lead is preferentially sequestered in the nucleus (Castellino and Aloj, 1964; Goyer et al., 1970) and mitochondrial fractions (Castellino and Aloj, 1964; Barltrop et al., 1974) of cells from lead-exposed animals. Lead enrichment in the mitochondrion is consistent with the high sensitivity of this organelle to the toxic effects of lead.

The neonatal animal seems to retain proportionately higher levels of tissue lead compared with the adult (Goldstein et al., 1974; Momcilović and Kostial, 1974; Mykkänen et al., 1979; Klein and Koch, 1981) and shows slow decay of brain lead levels while other tissue levels significantly decrease over time. This decay appears to result from enhanced entry by lead due to a poorly developed brain barrier system in the developing animals, as well as enhanced body retention in the young animals. The effects of such changes as metabolic stress and nutritional status have been noted in the literature. Keller and Doherty (1980b) have documented that tissue redistribution of lead, specifically bone lead mobilization, occurs in lactating female mice, with both lead and calcium transfer occurring from mother to pups (Keller and Doherty, 1980c). Changes in lead movement from body compartments, particularly bone, with changes in nutrition are described in Section 10.5.

In animal studies that are relevant both to the issue of chelatable lead versus lead indicators in humans and to the relative lability of lead in the young versus the adult, Jugo et al. (1975b) and Jugo (1980) studied the chelatability of lead in neonate versus adult rats and its lability in the erythrocyte. Challenging young rats with metal chelants yielded proportionately lower levels of urinary lead than in the adult, a finding that has been ascribed to tighter binding of lead in the young animal (Jugo et al., 1975b). In a related observation, the chelatable fraction of lead bound to erythrocytes of young animals given ^{203}Pb was approximately threefold greater than in the adult rat (Jugo, 1980), although the fraction of dose in the cells was higher in the suckling rat. The difference in the suckling rat erythrocyte regarding the binding of lead and relative content compared with the adult may be compared with Ong and Lee's (1980b) observation that human fetal hemoglobin binds lead more avidly than does mature hemoglobin.

10.4 LEAD EXCRETION AND RETENTION IN HUMANS AND ANIMALS

Dietary lead that is not absorbed in humans and animals passes through the GI tract and is eliminated with feces, as is the deposited fraction of air lead that is swallowed and not absorbed. Lead absorbed into the blood stream and not retained is excreted through the renal and GI tracts, the latter by biliary clearance. The amounts appearing in urine and feces appear to be a function of such factors as species, age, and differences in dosing.

10.4.1 Human Studies

Booker et al. (1969) found that ^{212}Pb injected into two adult volunteers led to initial appearance of the label in urine (4.4 percent of dose in 24 hr), then in both urine and feces in approximately equal amounts. By use of the stable isotope ^{204}Pb, Rabinowitz et al. (1973) reported that urinary and fecal excretion of the label amounted to 38 and 8 μg/day in adult subjects, accounting for 76 and 16 percent, respectively, of the measured recovery. Fecal excretion was thus approximately twice that of all the remaining modes of excretion: hair, sweat, and nails (8 percent).

Perhaps the most detailed study of lead excretion in adult humans was done by Chamberlain et al. (1978), who administered ^{203}Pb by injection, inhalation, and ingestion. After injection or oral intake, the amounts in urine (Pb-U) and feces (Pb-Fe, endogenous fecal lead) were compared for the two administration routes. Endogenous fecal lead was 50 percent of that in urine, or a 2:1 ratio of urinary to fecal lead. (Increased transit time was allowed for fecal lead to pass through the GI tract.)

Based on the metabolic balance and isotope excretion data of Kehoe (1961a,b,c), Rabinowitz et al. (1976), and Chamberlain et al. (1978), as well as on some recalculations of the Kehoe and Rabinowitz data by Chamberlain et al. (1978), short-term lead excretion amounts to 50-60 percent of the absorbed fraction, the balance moving primarily to bone with some subsequent fraction (approximately half) of this stored amount eventually being excreted. The rapidly excreted fraction was determined by Chamberlain et al. (1978) to have an excretion half-life of about 19 days. This value is consistent with the estimates of Rabinowitz et al. (1976), who expressed clearance in terms of mean-lives. Mean-lives are multiplied by ln 2 (0.693) to arrive at half-lives. The similarity of the blood ^{203}Pb half-life with that of body excretion noted by Chamberlain et al. (1978) indicates a steady rate of clearance from the body.

The age dependency of lead excretion rates in humans has not been well studied; all of the above lead excretion data involved only adults. Table 10-3 combines available data from adults (Rabinowitz et al., 1977; Thompson, 1971; Chamberlain et al., 1978) and infants (Ziegler et al., 1978) for purposes of comparison. Intake, urine, fecal, and endogenous fecal lead data from two studies on adults and one report on infants are used. For consistency in the adult data, 70 kg is used as an average adult weight, and a Pb-Fe:Pb-U ratio of 0.5 is used. Daily lead intake, absorption, and excretion values are expressed as μg/kg body weight. For the infant data, daily endogenous fecal lead excretion is calculated using the adult ratio as well as the extrapolated value of 1.5 μg/kg. The respiratory lead intake value for the infants is an upper value (0.2 μg/m^3), since Ziegler et al. (1978) found air lead to be <0.2 μg/m^3. Compared to the two representative adult groups, infants appear to have a lower total excretion rate, although the excretion of endogenous fecal lead may be higher than for adults.

In humans, the dependence of lead excretion rate on level of exposure has been studied in some detail by Chamberlain (1983), who used data from the published reports of King et al. (1979), Williams et al. (1969), Gross (1981), Devoto and Spinazzola (1973), Azar et al. (1975), and Chamberlain et al. (1978). Figure 10-6 reproduces Chamberlain's plots of urinary excretion rate for lead versus blood lead as provided in the various studies. Renal clearance of lead appears to increase as blood lead increases from 25 to 80 μg/dl, the highest blood value reported. Given the earlier discussion concerning the increased fractional partitioning of blood lead into plasma with increasing blood lead burden (see Section 10.3.1), one would anticipate an increasing renal excretion rate for lead over a broad range of blood lead.

TABLE 10-3. DAILY LEAD EXCRETION AND RETENTION DATA FOR ADULTS AND INFANTS

	Children[a]	Adult group A[b]	Adult group B[c]
Dietary intake (µg/kg)	10.76	3.63	3.86
Fraction of intake absorbed	0.46 (0.55)[d]	0.15[e]	0.15[e]
Diet lead absorbed (µg/kg)	4.95 (5.92)	0.54	0.58
Air lead absorbed (µg/kg)	0.20	0.21	0.11
Total absorbed lead (µg/kg)	5.15 (6.12)	0.75	0.68
Urinary lead excreted (µg/kg)	1.00	0.47	0.34
Ratio: urinary/absorbed lead	0.19 (0.16)	0.62	0.50
Endogenous fecal lead (µg/kg)	0.5 (1.56)[f]	0.24[g]	0.17[g]
Total excreted lead (µg/kg)	1.50 (2.56)	0.71	0.51
Ratio: total excreted/absorbed lead	0.29 (0.42)	0.92	0.75
Fraction of intake retained	0.34 (0.33)	0.01	0.04

[a] Ziegler et al. (1978).

[b] Rabinowitz et al. (1977).

[c] Thompson (1971) and estimates of Chamberlain et al. (1978).

[d] Each of the values in parentheses in this column is corrected for endogenous fecal lead at extrapolated value from Ziegler et al. (1978).

[e] Corrected for endogenous fecal lead (Pb-Fe = 0.5 x Pb-U).

[f] Extrapolated value of 1.56 for endogenous fecal Pb.

[g] Pb-Fe = 0.5 x Pb-U.

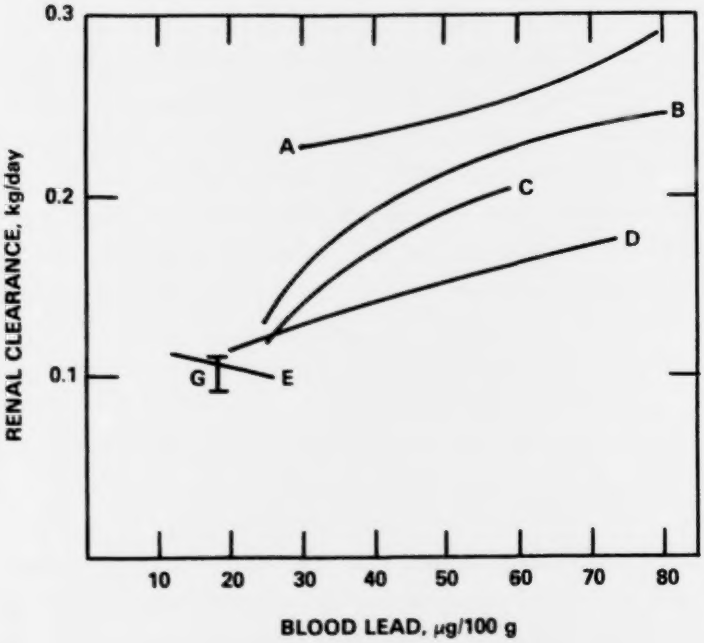


Figure 10-6. Renal clearance (ratio of urinary lead to blood lead) from (A) King et al., 1979; (B) Williams et al., 1969; (C) Gross, 1981; (D) DeVoto and Spinazzola, 1973; (E) Azar et al., 1975; (G) Chamberlain et al., 1978.

Source: Chamberlain (1983).

Data in Figure 10-6 indicate increased renal excretion of lead only. How the corresponding biliary excretion rate changes in the face of increasing lead absorption is not known. Hence, the overall impact of increasing exposure on total body clearance of the toxicant is difficult to assess. In experimental animals, the relative partitioning of lead between renal and biliary excretion routes has been shown to be dose- and species-dependent (see Section 10.4.2).

Lead accumulates in the human body with age, mainly in bone, up to approximately 60 years of age, when a decrease occurs with changes in intake as well as in bone mineral metabolism. Total accumulation by 60 years of age ranges up to approximately 200 mg (see review by Barry, 1978), although occupational exposure can raise this figure several-fold (Barry, 1975). Holtzman (1978) has reviewed the available literature on studies of lead retention in bone. In normally exposed humans a biological half-life of approximately 17 years has been calculated, while data for uranium miners yield a range of 1320-7000 days (4-19 years). Chamberlain et al. (1978) have estimated lifetime averaged daily retention at 9.5 µg using data of Barry (1975). Within shorter time frames, however, retention can vary considerably due to such factors as disruption of the individual's equilibrium with changes in level of exposure, the differences between children and adults, and, in elderly subjects, the presence of osteoporosis (Gross and Pfitzer, 1974).

Lead labeling experiments, such as those of Chamberlain et al. (1978), indicate a short-term or initial retention of approximately 40-50 percent of the fraction absorbed. Much of this retention is by bone. Determining how much lead resorption from bone will eventually occur using labeled lead is difficult, given the extremely small fraction of labeled to unlabeled lead (i.e., label dilution) that would exist. Based on the estimates of Kehoe (1961a,b,c), the Gross (1981) evaluation of the Kehoe studies, the Rabinowitz et al. (1976) study, the Chamberlain et al. (1978) assessments of the aforementioned reports, and the data of Thompson (1971), one can estimate that approximately 25 percent of the lead absorbed daily undergoes long-term bone storage.

The above estimates relate either to adults or to long-term retention over most of an individual's lifetime. Studies with children and developing animals (see Section 10.4.2) indicate lead retention in childhood can be higher than in adulthood. By means of metabolic balance studies, Ziegler et al. (1978) obtained a retention figure (as percentage of total intake) of 31.5 percent for infants, while Alexander et al. (1973) provided an estimate of 18 percent. Corrected retention data for both total and absorbed intake for the pediatric subjects of Ziegler et al. (1978) were shown in Table 10-3, using the two values for endogenous fecal excretion as noted. Barltrop and Strehlow (1978) calculated a net negative lead retention in their subjects, but problems in comparing this report with the others were noted earlier. Given the increased retention of lead in children relative to adults, as well as the greater rate of lead intake on a body-weight basis, increased uptake in soft tissues and/or bone is indicated.

Barry (1975, 1981) measured the lead content of soft and mineral tissues in a small group of autopsy samples from children 16 years of age and under, and noted that average soft-tissue values were comparable to those in female adults, while mean bone lead values were lower than in adults. These results suggest that bone in children has less retention capacity for lead than bone in adults. Note, however, that "dilution" of bone lead will occur because of the significant growth rate of the skeletal system through childhood. Trotter and Hixon (1974) studied changes in skeletal mass, density, and mineral content as a function of age, and noted that skeletal mass increases exponentially in children until the early teens, increases less up to the early 20s, levels off in adulthood, and then slowly decreases. From infancy to the late teens, bone mass increases up to 40-fold. Barry (1975) noted an approximate doubling in bone lead concentration over this interval, indicating that total skeletal lead had actually increased 80-fold. He also obtained a mean total bone lead content of approximately 8 mg for children up to 16 years old, compared with a value of approximately 18 mg estimated from both the bone concentrations in his study of children at different ages and the bone growth data of Trotter and Hixon (1974). In a later study (Barry, 1981), autopsy samples from infants and children between 1 and 9 years old showed an approximately 3.5-fold increase in mean bone concentrations across the three bone types studied, compared with a skeletal mass increase from 0-6 months to 3-13 years old of greater than 10-fold, for an estimated increase in total lead of approximately 35-fold. Five reports (see Barry, 1981) noted age versus tissue lead relationships indicating that overall bone lead levels in infants and children were less than in adults, whereas four reports observed comparable levels in children and adults.

If one estimates total daily retention of lead in the infants studied by Ziegler et al. (1978), using a mean body weight of approximately 10 kg and the corrected retention rate in Table 10-3, one obtains a total daily retention of approximately 40 μg. By contrast, the total reported or estimated skeletal lead accumulated between 2 and 14 years is 8-18 mg (vide supra), which averages out to a daily long-term retention of 2.0 to 4.5 μg/day or 6-13 percent of total retention. Lead retention may be highest in infants up to about 2 years of age (the subjects of the Ziegler et al. study), then decreases in older children. The mean retention in the Alexander et al. (1973) study was 18 percent, about half that seen by Ziegler et al. (1978). This difference may result from the greater age range in the former study.

"Normal" blood lead levels in children either parallel adult male levels or are approximately 30 percent greater than adult female levels (Chamberlain et al., 1978), indicating (1) that the soft-tissue lead pool in very young children is not greatly elevated and thus,

(2) that there is a huge labile lead pool in bone that is still kinetically quite distinct from soft-tissue lead or (3) that in young children, blood lead is a much less reliable indicator of greatly elevated soft-tissue or labile bone lead than is the case with adults. Barry (1981) found that soft-tissue lead levels were comparable in infants ≤1 year old and children 1-5 and 6-9 years old.

Given the implications of the above discussion--that retention of lead in young children is higher than in adults and possibly older children, while at the same time their skeletal system is less effective for long-term lead sequestration--the very young child is at greatly elevated risk to a toxicologically "active" lead burden. For further discussion, see Chapter 13.

Rabinowitz et al. (1976) examined the biokinetics of a stable isotope of lead (^{204}Pb) entering human hair after absorption, hair being a mode of lead excretion in humans and other mammals. Feeding adult male volunteers ^{204}Pb daily for about 100 days and analyzing the isotope in facial hair resulted in the observation that hair responds more gradually than blood to changes in uptake, with a delay of about 35 days. Hair lead values should be interpreted as the integral of the blood lead values over about 100 days.

10.4.2 Animal Studies

In rats and other experimental animals, both urinary and fecal excretion are important routes of lead removal from the organism. The relative partitioning between the two modes is species- and dose-dependent. Morgan et al. (1977) injected ^{203}Pb into adult rats and noted that lead initially appeared in urine, followed by equivalent elimination in both urine and feces. By 5 days, lead was proportionately higher in feces. Castellino and Aloj (1964), using ^{210}Pb, observed that fecal excretion was approximately twice that of urine (35.7 versus 15.9 percent) by 14 days. In the report of Klaassen and Shoeman (1974), relative excretion by the two routes was seen to be dose-dependent up to 1.0 mg Pb/kg. Excretion was much higher by biliary clearance into the gut. At 3.0 mg Pb/kg, approximately 90 percent of the excreted amount was detected in feces. The relatively higher proportion appearing in feces in the studies of Castellino and Aloj (1964) and Klaassen and Shoeman (1974), compared with the results of Morgan et al. (1977), possibly results from use of carrier dosing, since Morgan et al. (1977) used carrier-free injections. Hence, increasing dose does appear to favor biliary excretion, as noted by Klaassen and Shoeman (1974).

With regard to species differences, Klaassen and Shoeman (1974) found that the amount of biliary clearance in dogs was about 2 percent of that in rats, while rabbits showed 50 percent of the rate of the rat at equivalent dosing. These data for the dog conflict with the results of Lloyd et al. (1975), who observed 75 percent of the excreted lead eliminated through biliary clearance. Note that the latter researchers used carrier-free label while the other investigators used injections with carrier at levels of 3.0 mg Pb/kg. In mice, Keller and Doherty (1980a) observed that the cumulative excretion rate of ^{210}Pb in urine was 25-50 percent of that in feces. In nonhuman primates, Cohen (1970) observed that baboons excreted lead at the rate of 40 percent in feces and 60 percent in urine. Pounds et al. (1978) noted that the rhesus monkey lost 30 percent of lead by renal excretion and 70 percent by fecal excretion. This discrepancy may also reflect a carrier-dosing difference.

The extent of total lead excretion in experimental animals given labeled lead orally or parenterally varies, in part due to the time frames for post-exposure observation. In the adult rat, Morgan et al. (1977) found that 62 percent of injected ^{203}Pb was excreted by 6 days. By 8 days, 66 percent of injected ^{203}Pb was eliminated in the adult rats studied by Momcilović and Kostial (1974), while the ^{210}Pb excretion data of Castellino and Aloj (1964) for the adult rat showed 52 percent excreted by 14 days. Similar data were obtained by Klaassen and Shoeman (1974). Lloyd et al. (1975) found that dogs excreted 52 percent of injected lead label by 21 days, 83 percent by 1 year, and 87 percent by 2 years. In adult mice (Keller and Doherty, 1980a), 62 percent of injected lead label was eliminated by 50 days. In nonhuman primates, Pounds et al. (1978) measured approximately 18 percent excretion in adult rhesus monkeys by 4 days.

Kinetic studies of lead elimination in experimental animals indicate that excretion is described by two or more components. From the elimination data of Momcilović and Kostial (1974), Morgan et al. (1977) estimated that in the rat the excretion curve obeys a two-component exponential expression with half-lives of 21 and 280 hr. In dogs, Lloyd et al. (1975) found that excretion could be described by three components, i.e., a sum of exponentials with half-lives of 12 days, 184 days, and 4951 days. Keller and Doherty (1980a) reported that the half-life of whole-body clearance of injected ^{203}Pb consisted of an initial rapid and a much slower terminal component, the latter having a half-life of 110 days in the adult mouse.

The dependency of excretion rate on dose level has been investigated in several studies. Although Castellino and Aloj (1964) saw no difference in total excretion rate when label was injected with 7 or 100 µg of carrier, Klaassen and Shoeman (1974) did observe that the excretion rate by biliary tract was dose-dependent at 0.1, 1.0, and 3.0 mg Pb/kg (urine values were not provided for obtaining estimates of total excretion). Momcilović and Kostial (1974) observed an increased rate of excretion into urine over the added carrier range of 0.1 to 2.0 µg Pb/kg with no change in fecal excretion. In the report of Aungst et al. (1981), excretion rate in the rat did not change over the injected lead dosing range of 1.0 to 15.0 mg/kg. Rat urinary excretion rates thus seem dose-dependent over a narrow range less than 7 µg, while elimination of lead through biliary clearance is dose-dependent up to an exposure level of 3 mg/kg.

Lead movement from lactating animals to their offspring via milk constitutes both a route of excretion for the mother and a route of exposure for the young. Investigations directed at this phenomenon have examined both prior-plus-ongoing maternal lead exposure during lactation and the effects of immediate prior treatment. Keller and Doherty (1980b) exposed two groups of female rats to ^{210}Pb: one group for 105 days before mating; the second before and during gestation and nursing. During lactation, there was an overall loss of lead from the bodies of the lactating females compared with controls, while the femur ash weights were inversely related to level of lead excretion, indicating that such enhancement is related to bone mineral metabolism. Lead transfer via milk was approximately 3 percent of maternal body burden, increasing with continued lead exposure during lactation. Lorenzo et al. (1977) found that blood lead levels in nursing rabbits given injected lead peaked rather rapidly (within 1 hr), while milk lead levels showed a continuous increase for about 8 days, at which point the concentration of lead was eightfold higher than in blood. This observation indicates that the transfer of lead to milk can occur against a concentration gradient in blood. Momcilović (1978) and Kostial and Momcilović (1974) observed that transfer of ^{203}Pb in the late stage of lactation occurs readily in the rat, with higher overall excretion of lead in nursing versus control females. Furthermore, the rate of lead movement to milk appeared dose-dependent over the added lead carrier range of 0.2 to 2.0 µg.

The comparative retention of lead in developing versus adult animals has been investigated in several studies using rats, mice, and nonhuman primates. Momcilović and Kostial (1974) compared the kinetics of lead distribution in suckling and adult rats after injection of ^{203}Pb. Over an 8-day interval, 85 percent of the label was retained in the suckling rat, compared with 34 percent in the adult. Keller and Doherty (1980a) compared the levels of ^{210}Pb in 10-day-old mice and adults, noting from the clearance half-lives (vide supra) that lead retention was greater in the suckling animals than in the adults. In both adult and young mice, the rate of long-term retention was governed by the rate of release of lead from bone, indicating that in the mouse, skeletal lead retention in the young is greater than in the adult. With infant and adult monkeys orally exposed to ^{210}Pb, Pounds et al. (1978) observed that at 23 days the corresponding amounts of initial dose retained were 92.7 and 81.7 percent, respectively.

The studies of Rader et al. (1981a,b) are of particular interest because they demonstrate not only that young experimental animals continue to show greater retention of lead in tissue when exposure occurs after weaning, but also that such retention occurs in terms of either uniform exposure (Rader et al., 1981a) or uniform dosing (Rader et al., 1981b) when compared with adult animals. With uniform exposure, 30-day-old rats given lead in drinking water showed significantly higher lead levels in blood and higher percentages of dose retained in brain, femur, and kidney, as well as higher indices of hematopoietic impairment (ALA in urine, erythrocyte porphyrin) when compared to adult animals. As a percentage of dose retained, levels of lead retained in the tissue of the young animals were approximately two- to threefold higher. In part, this difference results from a higher ingestion rate of lead. However, in the uniform dosing study where a higher ingestion rate was not the case, an increased retention of lead still prevailed, the amount of lead in brain being approximately 50 percent higher in young versus adult animals. Comparison of values in terms of percent retained is more meaningful for such assessments, because the factor of changes in organ mass (see above) is taken into account. Delayed excretion of lead in the young animal may reflect an immature excretory system or a tighter binding of lead in various body compartments.

10.5 INTERACTIONS OF LEAD WITH ESSENTIAL METALS AND OTHER FACTORS

Deleterious agents, particularly toxic metals such as lead, do not express their toxicokinetic or toxicological behavior in a physiological vacuum, but rather are affected by interactions of the agent with a variety of biochemical factors such as nutrients. Growing recognition of this phenomenon and its implications for lead toxicity in humans has prompted a number of studies, many of them recent, that address both the scope and mechanistic nature of such interactive behavior.

Taken collectively, the diverse human and animal data described in this section make it clear that there is heterogeneity in pediatric populations in terms of relative risk for lead exposure and deleterious effects depending on nutritional status. Children having multiple nutrient deficiencies are at greater risk.

10.5.1 Human Studies

In humans, the interactive behavior of lead and various nutritional factors is appropriately viewed as particularly significant for children, since this age group is not only particularly sensitive to lead's effects, but also experiences the greatest flux in relative nutrient status. Such interactions occur against a backdrop of rather widespread deficiencies in a number of nutritional components in children. While such deficiencies are more pronounced in lower-income groups, they exist in all socioeconomic strata. Mahaffey and Michaelson (1980) have summarized the three national nutritional status surveys carried out in the United States for infants and young children: the Preschool Nutrition Survey, the Ten State Nutrition Survey, and the Health Assessment and Nutrition Evaluation Survey (HANES I). The most recent body of data of this type is the second National Health Assessment and Nutrition Evaluation Survey (NHANES II) study (Mahaffey et al., 1979), although the dietary information from it has yet to be reported. In the older surveys, iron deficiency was the most common nutritional deficit in children under 2 years of age, particularly children from low-income groups. Reduced vitamin C intake was noted in about one-third of the children, while sizable numbers of them had significantly reduced intakes of calcium. Owen and Lippman (1977) reviewed the regional surveys of low-income groups within Hispanic, white, and black populations. In these groups, iron deficiency was a common finding, and low intakes of calcium and vitamins A and C were observed regularly. Hambidge (1977) concluded that zinc intake in low-income groups is generally inadequate relative to recommended daily allowances.

Available data from a number of reports document the association of lead absorption with suboptimal nutritional status. Mahaffey et al. (1976) summarized their studies showing that children with blood lead levels greater than 40 μg/dl had significantly ($p < 0.01$) lower intake of phosphorus and calcium compared with a control group, while iron intake in the two groups was comparable. This study involved children 1-4 years old from an inner-city, low-income population, with close matching for all parameters except the blood lead level. Sorrell et al. (1977), in their nutritional assessment of 1- to 4-year-old children with a range of blood lead levels, observed that blood lead content was inversely correlated with calcium intake, while children with blood lead levels >60 μg/dl had significantly ($p < 0.001$) lower intakes of calcium and vitamin D.

Rosen et al. (1980, 1981) found that children with elevated blood lead (33-120 μg/dl) had significantly lower serum concentrations of the vitamin D metabolite 1,25-dihydroxyvitamin D (1,25-$(OH)_2D$) compared with age-matched controls ($p < 0.001$), and showed a negative correlation of serum 1,25-$(OH)_2D$ with lead over the range of blood lead levels measured (see Chapter 12, Section 12.5, for further discussion). These observations and animal data (Barton et al., 1978a; see Section 10.5.2) may suggest an increasingly adverse interactive cycle of 1,25-$(OH)_2D$, lead, and calcium in which lead reduces biosynthesis of the vitamin D metabolite. This cycle leads to reduced induction of calcium binding protein (CaBP), less absorption of calcium from the gut, and greater uptake of lead, thus further reducing metabolite levels. Barton et al. (1978a) isolated two mucosal proteins in rat intestine, one of which bound mainly lead and was not vitamin D-stimulated. The second bound mainly calcium and was under vitamin control. The authors suggested direct site-binding competition between lead and calcium in these proteins. Hunter (1978) investigated the possible interactive role of seasonal vitamin D biosynthesis in adults and children; lead poisoning occurs more often in summer than in other seasons (see Hunter, 1977, for review). Seasonality accounts for 16 percent of explained variance of blood lead levels in black children, 12 percent in Hispanic children, and 4 percent in white children. More recently, it has been documented that there is no seasonal variation in circulating levels of 1,25-$(OH)_2D$, the metabolite that affects the rate of lead absorption from the GI tract (Chesney et al., 1981). These results suggest that seasonality is related to changes in exposure.

Johnson and Tenuta (1979) determined that calcium intake was negatively correlated ($r = -0.327$, $p < 0.05$) with blood lead in 43 children aged 1-6 years. The high lead group consumed less zinc than children with lower blood levels. Yip et al. (1981) found that 43 children with elevated blood lead (>30 µg/dl) and erythrocyte protoporphyrin (EP) (>35 µg/dl) had an increased prevalence of iron deficiency as these two parameters increased. Children classed in CDC categories Ib and II had a 79 percent iron deficiency rate, while those in Class III were all iron deficient. Chisolm (1981) demonstrated an inverse relationship between chelatable iron and chelatable body lead levels as indexed by urinary ALA levels in 66 children with elevated blood lead. Watson et al. (1980) reported that adult subjects who were iron deficient (determined from serum ferritin measurement) showed a lead absorption rate 2-3 times greater than subjects who were iron replete. In a group of 13 children, Markowitz and Rosen (1981) reported that the mean serum zinc levels in children with plumbism were significantly below the values seen in normal children. Chelation therapy reduced the mean level even further. Chisolm (1981) reported an inverse relationship between ALA in urine (ALA-U) and the amount of chelatable or systemically active zinc in 66 children challenged with EDTA and having blood lead levels ranging from 45 to 60 µg/dl. These two studies suggest that zinc status is probably as important an interactive modifier of lead toxicity as is either calcium or iron.

The role of nutrients in lead absorption has been reported in several metabolic balance studies for both adults and children. Ziegler et al. (1978), in their investigations of lead absorption and retention in infants, observed that lead retention was inversely correlated with calcium intake, expressed either as a percentage of total intake ($r = -0.284$, $p < 0.01$) or on a weight basis ($r = -0.279$, $p < 0.01$). Interestingly, the calcium intake range measured was within the range considered adequate for infants and toddlers by the National Research Council (National Academy of Sciences, National Research Council, 1974). These data also support the premise that severe deficiency need not be present for an interactive relationship to occur. Using adults, Heard and Chamberlain (1982) monitored the uptake of ^{203}Pb from the gut in eight subjects as a function of the amounts of dietary calcium and phosphorus. Without supplementation of these minerals in fasting subjects, the label absorption rate was approximately 60 percent, compared to 10 percent with 200 mg calcium plus 140 mg phosphorus, the amounts present in an average meal. Calcium alone reduced uptake by a factor of 1.3 and phosphorus alone by 1.2; both together yielded a reduction factor of 6. This work suggests that insoluble calcium phosphate is formed and co-precipitates any lead present. This interpretation is supported by animal data (see Section 10.5.2).

10.5.2 Animal Studies

Reports of lead-nutrient interactions in experimental animals have generally described such relationships in terms of a single nutrient, using relative absorption or tissue retention in the animal to index the effect. Most of the recent data are concerned with the impact of dietary levels of calcium, iron, phosphorus, and vitamin D. Furthermore, some investigators have attempted to elucidate the site(s) of interaction as well as the mechanism(s) governing the interactions. Lead's interactions involve the effect of the nutrient on lead uptake, as well as lead's effect on nutrients. The focus of this discussion is on the former. These interaction studies are tabulated in Table 10-4.

10.5.2.1 Interactions of Lead with Calcium. The early report of Sobel et al. (1940) noted that variation of dietary calcium and other nutrients affected the uptake of lead by bone and blood in animals. Subsequent studies by Mahaffey-Six and Goyer (1970) in the rat have demonstrated that a considerable reduction in dietary calcium was necessary (from 0.7 percent to 0.1 percent), at which level blood lead was increased fourfold, kidney lead content was elevated 23-fold, and relative toxicity (Mahaffey et al., 1973) was increased. The changes in calcium necessary to alter lead's effects in the rat appear to be greater than those seen by Ziegler et al. (1978) in young children, which indicates a species difference in terms of sensitivity to basic dietary differences as well as to levels of all interactive nutrients. These observations in the rat have been confirmed by Kostial et al. (1971), Quarterman and Morrison (1975), Barltrop and Khoo (1975), and Barton et al. (1978a). The inverse relationship between dietary calcium and lead uptake has also been noted in the pig (Hsu et al., 1975), horse (Willoughby et al., 1972), lamb (Morrison et al., 1977), and domestic fowl (Berg et al., 1980).

The mechanism(s) governing lead's interaction with calcium operate at both the gut wall and within body compartments. Barton et al. (1978a), using everted duodenal sac preparations in the rat, reported the following: (1) interactions at the gut wall require the presence of intubated calcium to affect lead label absorption (pre-existing calcium deficiency in the animal and no added calcium had no effect on lead transport); (2) calcium-deficient animals show increased retention of lead rather than absorption (confirmed by Quarterman et al., 1973); and (3) lead transport may be mediated by two mucosal proteins, one of which has high molecular weight and a high proportion of bound lead, and is affected in extent of lead binding with changes in lead uptake. The second protein binds mainly calcium and is vitamin D-dependent.

Smith et al. (1978) found that lead is taken up at a different site in the duodenum of rats than is calcium, but absorption does occur at the site of phosphate uptake, suggesting a complex interaction of phosphorus, calcium, and lead. This observation is consistent with the data of Barltrop and Khoo (1975) for rats and the data of Heard and Chamberlain (1982) for

TABLE 10-4. EFFECT OF NUTRITIONAL FACTORS ON LEAD UPTAKE IN ANIMALS

Factor	Species	Index of effect	Interactive effect	Reference
Calcium	Rat	Lead in tissues and effect severity at low levels of dietary calcium	Low dietary calcium (0.1%) increases lead absorption and severity of effects	Mahaffey-Six and Goyer (1970); Mahaffey et al. (1973)
Calcium	Pig	Lead in tissues at low levels of dietary calcium	Increased absorption of lead with low dietary calcium	Hsu et al. (1975)
Calcium	Horse	Lead in tissues at low levels of dietary calcium	Increased absorption of lead with low dietary calcium	Willoughby et al. (1972)
Calcium	Lamb	Lead in tissues at low levels of dietary calcium	Increased absorption of lead with low dietary calcium	Morrison et al. (1977)
Calcium	Rat	Lead retention	Retention increased in calcium deficiency	Barton et al. (1978a)
Iron	Rat	Tissue levels and relative toxicity of lead	Iron deficiency increases lead absorption and toxicity	Mahaffey-Six and Goyer (1972)
Iron	Rat	Lead absorption in everted duodenal sac preparation	Reduction in intubated iron increases lead absorption; increased levels decrease lead uptake	Barton et al. (1978b)
Iron	Mouse	Lead retention	Iron deficiency has no effect on lead retention	Hamilton (1978)

TABLE 10-4. (continued)

Factor	Species	Index of effect	Interactive effect	Reference
Iron	Rat	*In utero* or milk transfer of lead in pregnant or lactating rats	Iron deficiency increases both *in utero* and milk transfer of lead to sucklings	Cerklewski (1980)
Phosphorus	Rat	Lead uptake in tissues	Reduced phosphorus increased ^{203}Pb uptake 2.7-fold	Barltrop and Khoo (1975)
Phosphorus	Rat	Lead retention	Low dietary phosphorus enhances lead retention; no effect on lead resorption in bone	Quarterman and Morrison (1975)
Phosphorus	Rat	Lead retention	Low dietary phosphorus enhances both lead retention and deposition in bone	Barton and Conrad (1981)
Vitamin D	Rat	Lead absorption using everted sac techniques	Increasing vitamin D increases intubated lead absorption	Smith et al. (1978)
Vitamin D	Rat	Lead absorption using everted sac techniques	Both low and excess levels of vitamin D increase lead uptake by affecting motility	Barton et al. (1980)
Lipid	Rat	Lead absorption	Increases in lipid (corn oil) content up to 40% enhance lead absorption	Barltrop and Khoo (1975)
Protein	Rat	Lead uptake by tissues	Both low and high protein in diet increase lead absorption	Barltrop and Khoo (1975)

TABLE 10-4. (continued)

Factor	Species	Index of effect	Interactive effect	Reference
Protein	Rat	Body lead retention	Low dietary protein either reduces or does not affect retention in various tissues	Quarterman et al. (1978b)
Protein	Rat	Tissue levels of lead	Casein in diet increases lead uptake compared to soybean meal	Anders et al. (1982)
Milk components	Rat	Lead absorption	Lactose-hydrolyzed milk does not increase lead absorption, but ordinary milk does	Bell and Spickett (1981)
Milk components	Rat	Lead absorption	Lactose in diet enhances lead absorption compared to glucose	Bushnell and DeLuca (1981)
Zinc	Rat	Lead absorption	Low zinc in diets increases lead absorption	Cerklewski and Forbes (1976); El-Gazzar et al. (1978)
Zinc	Rat	Lead transfer *in utero* and in milk during lactation	Low-zinc diet of mother increases lead transfer *in utero* and in maternal milk	Cerklewski (1979)
Zinc	Rat	Tissue retention	Low zinc diet enhances brain Pb levels	Bushnell and Levin (1983)
Copper	Rat	Lead absorption	Low copper in diet increases lead absorption	Klauder et al. (1973); Klauder and Petering (1975)

humans. Thus, the combined action of the two mineral nutrients is greater than the sum of their individual effects.

Mykkänen and Wassermann (1981) observed that lead uptake in the intestine of the chick occurs in two phases: a rapid uptake (within 5 min) followed by a rate-limiting slow transfer of lead into blood. Conrad and Barton (1978) have observed a similar process in the rat. Hence, either a saturation process occurs (i.e., carrier-mediated transport) or lead simply precipitates in the lumen. In the former case, calcium interacts to saturate the carrier proteins as isolated by Barton et al. (1978a) or may precipitate lead in the lumen by initial formation of calcium phosphate.

Quarterman et al. (1978a) observed that calcium supplementation of the diet above normal also resulted in increased body retention of lead in the rat. Because both deficiency (Barton et al., 1978a) and excess in calcium intake enhance retention, two sites of influence on retention are suggested. Goyer (1978) has suggested that body retention of lead in calcium deficiency, i.e., reduced excretion rate, may result from renal impairment, while Quarterman et al. (1978a) suggest that excess calcium suppresses calcium resorption from bone, hence also reducing lead release.

10.5.2.2 Interactions of Lead with Iron. Mahaffey-Six and Goyer (1972) reported that iron-deficient rats had increased tissue levels of lead and manifested greater toxicity compared with control animals. This uptake change was seen with but minor alterations in hematocrit, indicating a primary change in lead absorption over the time of the study. Barton et al. (1978b) found that dietary restriction of iron, using ^{210}Pb and everted sac preparations in the rat, led to enhanced lead absorption, whereas iron loading suppressed the extent of lead uptake, using normal intake levels of iron. This suppression suggests receptor-binding competition at a common site, consistent with the isolation by these workers of two iron-binding mucosa fractions. While the iron level of diet affects lead absorption, the effect of changes in lead content in the gut on iron absorption is not clear. Barton et al. (1978b) and Dobbins et al. (1978) observed no effect of lead in the gut on iron absorption in the rat, while Flanagan et al. (1979) reported that lead reduced iron absorption in mice.

In the mouse, Hamilton (1978) found that body retention of ^{203}Pb was unaffected by iron deficiency, using intraperitoneal administration of the label, while gastric intubation did lead to increased retention. Animals with adequate iron showed no changes in lead retention at intubation levels of 0.01 to 10 nM. Cerklewski (1980) observed that lead transfer both *in utero* and in milk to nursing rats was enhanced compared with controls when dams were maintained from gestation through lactation on low-iron diets.

10.5.2.3 Lead Interactions with Phosphate. The early studies of Shelling (1932), Grant et al. (1938), and Sobel et al. (1940) documented that dietary phosphate influenced the extent of lead toxicity and tissue retention of lead in animals. Low levels of phosphate enhanced these parameters, while excess intake retarded the effects. More recently, Barltrop and Khoo (1975) reported that reduced phosphate increased the uptake of ^{203}Pb approximately 2.7-fold compared with controls. Quarterman and Morrison (1975) found that low dietary phosphate enhanced lead retention in rats but had no effect on skeletal lead mobilization, nor was injected lead label affected by such restriction. In a related study, Quarterman et al. (1978a) found that doubling the nutrient over normal levels resulted in lowering lead absorption by approximately half. Barton and Conrad (1981) found that reduced dietary phosphorus increased the retention of labeled lead and deposition in bone, in contrast to the results of Quarterman and Morrison (1975). Increasing the intraluminal level of phosphorus reduced lead absorption, possibly by increasing intraluminal precipitation of lead as the mixed lead/calcium phosphate. Smith et al. (1978) reported that lead uptake occurs at the same site as phosphate, suggesting that lead absorption may be more related to phosphate than calcium transport.

10.5.2.4 Interactions of Lead with Vitamin D. Several studies had earlier indicated that a positive relationship might exist between dietary vitamin D and lead uptake, resulting in either greater manifestations of lead toxicity or a greater extent of lead uptake (Sobel et al., 1938, 1940). Using the everted sac technique and testing with ^{210}Pb, Smith et al. (1978) observed that increasing levels of intubated vitamin D in the rat resulted in increased absorption of the label, with uptake occurring at the distal end of the rat duodenum, the site of phosphorus uptake and greatest stimulation by the vitamin. Barton et al. (1980) used ^{210}Pb to monitor lead absorption in the rat under conditions of normal, deficient, and excess amounts of dietary vitamin D. Lead absorption is increased with either low or excess vitamin D. This increased absorption apparently occurs as a result of increased retention time of fecal mass containing the lead due to alteration of intestinal motility rather than as a result of direct enhancement of mucosal uptake rate. Hart and Smith (1981) reported that vitamin D repletion of diet enhanced lead absorption (^{210}Pb) in the rat, while also enhancing femur and kidney lead uptake when the label was injected.

10.5.2.5 Interactions of Lead with Lipids. Barltrop and Khoo (1975) observed that varying the lipid (corn oil) content of rat diet from 5 up to 40 percent resulted in an increase of lead in blood 13.6-fold higher than the normal level. Concomitant increases were observed in lead levels in kidney, femur, and carcass. Reduction of dietary lipid below the 5 percent control figure did not affect the lead-absorption rate. As an extension of this earlier work, Barltrop (1982) has noted that the chemical composition of the lipid is a significant factor in affecting lead absorption. Study of triglycerides of saturated and unsaturated fatty acids showed that polyunsaturated trilinolein increased lead absorption by 80 percent in rats, when given as 5- or 10-percent loadings in diet, compared with monounsaturated triolein or any of the saturates in the series tricaproin to tristearin.

10.5.2.6 Lead Interaction with Protein. Quarterman et al. (1978b) have drawn attention to one of the inherent difficulties of measuring lead-protein interactions, i.e., the effect of protein on both growth and the toxicokinetic parameters of lead. Der et al. (1974) found that reduction of dietary protein, from 20 to 4 percent, led to increased uptake of lead in rat tissues, but the approximately sixfold reduction in body weight over the interval of the study makes it difficult to draw any firm conclusions. Barltrop and Khoo (1975) found that ^{203}Pb uptake by rat tissue could be enhanced with either suboptimal or excess levels of protein in diet. Quarterman et al. (1978b) reported that retention of labeled lead in rats maintained on a synthetic diet containing approximately 7 percent protein was either unaffected or reduced compared with controls, depending on tissues taken for study.

Not only levels of protein but also the type of protein appears to affect tissue lead levels. Anders et al. (1982) found that rats maintained on either of two synthetic diets varying only by having casein or soybean meal as the protein source showed significantly higher lead levels in the casein group.

10.5.2.7 Interactions of Lead with Milk Components. For many years, milk was recommended as a counteractant for lead poisoning among lead workers (Stephens and Waldron, 1975). More recent data, however, pose a mixed picture. Kello and Kostial (1973) found that rats maintained on milk diets absorbed a greater amount of ^{203}Pb than those fed commercial rat chow. This phenomenon was ascribed to relatively lower levels of certain nutrients in milk compared with the rat chow. These observations were confirmed by Bell and Spickett (1981), who also observed that lactose-hydrolyzed milk was less effective than the ordinary form in promoting lead absorption, suggesting that lactose may be the enhancing agent. Bushnell and DeLuca (1981) demonstrated that lactose significantly increased ^{210}Pb absorption and tissue retention by weanling rats when given in high doses by intubation. However, lactose levels close to usual dietary content actually have an inhibiting effect on lead absorption (Bushnell and DeLuca, 1983). In human studies, moreover, milk consumption is inversely related to blood lead levels, suggesting a net protective effect (Johnson and Tenuta, 1979; Brunekreef et al., 1983).

10.5.2.8 Lead Interactions with Zinc and Copper. The studies of Cerklewski and Forbes (1976) and El-Gazzar et al. (1978) documented that zinc-deficient diets promote lead absorption in the rat, while repletion with zinc reduces lead uptake. The interaction continues within the body, particularly with respect to ALA-D activity (see Chapter 12, Section 12.3.1.2). In a study of zinc-lead interactions in female rats during gestation and lactation, Cerklewski (1979) observed that zinc-deficient diets resulted in more transfer of lead through milk to the pups as well as reduced litter body weights. Bushnell and Levin (1983) have shown that rats fed a low-zinc diet (2.0 ppm) containing lead at levels of 10 or 100 ppm had significantly higher retention of lead in brain and calvarium compared to those fed a diet with 20 ppm zinc. Victery and coworkers (1981) evaluated the acute effects of lead on the behavior of renal and plasma zinc in the dog. They found that lead enhanced urinary zinc excretion and was related to both increased ultrafilterable plasma zinc and a change in renal tubular zinc transport.

Klauder et al. (1973) reported that low dietary copper enhanced lead absorption in rats fed a high-lead diet (5000 ppm). These observations were confirmed by Klauder and Petering (1975) at a level of 500 ppm lead in diet. The same researchers subsequently observed that reduced copper enhanced the hematological effects of lead (Klauder and Petering, 1977), and that both copper and iron deficiencies must be corrected to restore hemoglobin levels to normal.

10.6 INTERRELATIONSHIPS OF LEAD EXPOSURE, EXPOSURE INDICATORS, AND TISSUE LEAD BURDENS

Information presented so far in this chapter sets forth the quantitative and qualitative aspects of lead toxicokinetics, including the compartmental modeling of lead distribution _in vivo_, and leads up to the critical issue of the various interrelationships of lead toxicokinetics to lead exposure, toxicant levels in indicators of such exposure, and exposure-target tissue burdens of lead.

Chapter 11 (Sections 11.4, 11.5, 11.6) discusses the various experimental and epidemiological studies relating the relative impact of various routes of lead exposure on blood lead levels in human subjects, and includes a description of mathematical models for such relationships. In these sections, the basic question is: what is the mathematical relationship of lead in air, food, water, etc., to lead in blood? This question is descriptive and does not address the biological basis of the observed relationships. Nor does it consider the implications for adverse health risks in the sequence leading from external lead exposure to lead in some physiological indicator to lead in target tissues.

For purposes of discussion, this section separately considers (1) the temporal characteristics of physiological indicators of lead exposure, (2) the biological aspects of the relationship of external exposure to internal indicators of exposure, and (3) internal indicator-tissue lead relationships, including both steady-state lead exposure and abrupt changes in lead exposure. The relationship of internal indicators of body lead, such as blood lead, to biological indicators such as EP or ALA-U is discussed in Chapter 13.

10.6.1 Temporal Characteristics of Internal Indicators of Lead Exposure

The biological half-life for blood lead or the nonretained fraction of body lead is generally assumed to be rather short, although it in fact depends upon the mobile lead body burden (O'Flaherty et al., 1982; also see Sections 10.3 and 10.4). Nevertheless, a given blood or urine lead value reflects rather recent exposure compared to tooth or bone lead values. In cases where lead exposure can be reliably assumed to have occurred at a given level, a blood lead value is more useful than in cases where some intermittent, high level of exposure may have occurred. The former most often occurs with occupational exposure, while the latter is of particular relevance to young children.

Reports have appeared dealing with the stability of individuals' blood lead levels over time under conditions of ambient exposure. David et al. (1982) followed 29 children, 4-12 years old, with monthly measurements and found the stability to be of a relatively high order (Pearson correlation coefficients of 0.7-0.8). Rabinowitz et al. (1984) sampled more than 200 infants semiannually from birth to 2 years of age and found average changes of about 4 μg/dl. Only 40 percent of these children tended to remain in their previous blood lead category (quartile). Within this age range, however, there was a trend toward less fluctuation with increasing age of the young child. Delves et al. (1984) followed 21 adults over 7-11 months with multiple blood lead measurements and found little fluctuation over time (about 1 μg/dl or less, on average). Hence, there appears to be increasing stability with relatively constant exposure as the individual increases in age.

Accessible mineralizing tissue, such as shed teeth, extend the time frame for assessing lead exposure from months to years (Section 10.3), since teeth accumulate lead up to the time of shedding or extraction. Levels of lead in teeth increase with age in proportion to exposure (Steenhout and Pourtois, 1981). Furthermore, tooth lead levels are correlated with blood lead levels in humans (Shapiro et al., 1978) and animals (Kaplan et al., 1980). The technique of Fremlin and Edmonds (1980), employing microautoradiography of irradiated teeth, permits the identification of dentine zones high in lead content, thus allowing the disclosure of past periods of abrupt increases in lead intake.

While levels of lead in shed teeth are more valuable than blood lead levels in assessing exposure at more remote time points, such information is retrospective in nature and would not be of use in monitoring current exposure. In this case, serial blood lead measurements must be employed. With the development of methodology for *in situ* measurement of tooth lead in children (described in Chapter 9), serial *in situ* tooth analysis in tandem with serial blood lead determination would provide comparative data for determining both time-concordant blood/tooth lead relationships as well as which measure is the better indicator of ongoing exposure. Given the limitations of an indicator such as blood lead in reflecting lead uptake in target organs, as discussed below, the rate of accumulation of lead in teeth measured *in situ* may well be a better index of ongoing tissue lead uptake. This aspect merits further study, especially since Shapiro et al. (1978) were able to demonstrate the feasibility of using *in situ* tooth lead analysis in a large group of children screened for lead exposure.

10.6.2 Biological Aspects of External Exposure/Internal Indicator Relationships

Information provided in Chapter 11 as well as the critiques of Hammond et al. (1981) and Brunekreef (1984) indicate that the relationship of lead levels in air, food, and water to lead levels in blood is curvilinear, with the result that as "baseline" blood lead rises (i.e., as one moves up the curve), the relative change in the dependent variable, blood lead, per unit change of lead in some intake medium (such as air) becomes smaller. Conversely, as one proceeds down the curve with reduction in "baseline" lead, the corresponding change in blood lead becomes larger. One assumption in this "single medium" approach is that the baseline is not integrally related to the level of lead in the particular medium being studied. This assumption is not necessarily appropriate for air versus food lead, nor, in the case of young children, for air lead versus total oral intake of the element. However, it should be noted that Hammond et al. (1981) assigned virtually all of the body compartment lead to the blood, giving blood lead levels in their modeling scheme that were too high. The authors recognized this and later offered a qualification (Hammond et al., 1982).

Hammond et al. (1981) have also noted that the shape of the blood lead curves seen in human subjects is similar to that discernible in certain experimental animal studies with dogs, rats, and rabbits (Azar et al., 1973; Prpić-Majić et al., 1973). Similarly, Kimmel et al. (1980), after exposing adult female rats to lead at four levels in drinking water for 6-7 weeks, found values of blood lead that showed a curvilinear relationship to the dose levels. Over the dosing range of 5 to 250 ppm in water, the blood lead range was 8.5 to 31 μg/dl. In a related study (Grant et al., 1980) rats were exposed to lead *in utero*, through weaning, and up to 9 months of age at the dosing range used in the Kimmel et al. study (0.5 to 250 ppm in the dams' drinking water until weaning of pups, then the same levels in the weanlings' drinking water). These animals showed a blood lead range of 5 to 67 μg/dl. One may assume that in all of the above studies the lead in the various dosing groups was near or at equilibrium within the various body compartments.

The biological basis of the curvilinear relationship of blood lead to lead intake, across a broad range of blood lead values, may result from a number of factors. In lead workers, as a specific case, increasing workplace air lead level is associated with an increased particle aggregation rate leading to a lowering of the effective fraction of respirable, submicrometer particles, as suggested by Chamberlain (1983). In studies with human volunteers, there appears to be no change in respiratory absorption rate at lung lead burdens up to 450 μg (Chamberlain et al., 1978). It was noted earlier that oral lead intake up to 400 μg in adults is associated with unaltered absorption rate. However, animal data relevant to this question indicate that dietary levels between 10 and 100 ppm lead are associated with a decreased absorption rate (Bushnell and DeLuca, 1983). If these data were applied directly to humans, a daily intake rate of 20-200 mg lead would be required to produce a similar decrease.

The curvilinear blood lead/diet lead relationship may or may not be independent of GI absorption rate. The experimental animal studies of Prpić-Majić et al. (1973) indicated a curvilinear relationship of blood lead to dose of lead when the toxicant was administered by injection to rabbits. On the other hand, injection of higher doses into rats does show a linear relationship (Aungst et al., 1981).

The data of DeSilva (1981), Manton and Malloy (1983), and Manton and Cook (1984) all suggest that the increasingly greater fraction of lead in plasma as blood lead increases may be significant (see Section 10.3.1). This increase of lead in plasma would indicate a relatively greater movement of lead from plasma to tissues and a higher excretion rate, both of which serve to modulate the rate of rise of the whole blood lead with increasing circulating lead. These results are consistent with the report of Chamberlain (1983) showing an apparent increased urinary excretion rate of lead with rising blood lead. They are also in accord with the observations that tissue lead burdens show a better proportionality to exposure level than does blood lead burden (see Section 10.3.1). Since an increased movement of plasma lead to tissues with increasing blood lead burden would also include deposition in bone, the curvilinear relationship of chelatable lead to blood lead may also be influenced by the plasma/blood relationship.

10.6.3 Internal Indicator/Tissue Lead Relationships

In living human subjects, to determine tissue lead burdens directly (or relate these levels to adverse effects associated with target tissue) as a function of lead intake is not possible. Instead, measurement of lead in an accessible indicator such as blood, along with determination of some biological indicator of impairment (e.g., ALA-U or EP), is used.

Evidence continues to accumulate in both the clinical and experimental animal literature that the use of blood lead as an indicator can have limitations in reflecting both the amounts of lead in target tissues and the temporal changes in tissue lead with changes in exposure. Perhaps the best example of the problem is the relationship of blood lead to chelatable lead (see Section 10.3.3). Currently, measurement of the plumburesis associated with challenge by a single dose of a chelating agent such as $CaNa_2EDTA$ is considered the best measure of the mobile, potentially toxic fraction of body lead in children and adults (Vitale et al., 1975; Wedeen et al., 1975; Chisolm et al., 1976; U.S. Centers for Disease Control, 1978; Chisolm and Barltrop, 1979; Hansen et al., 1981).

Chisolm et al. (1976) have documented that the relationship of blood lead to chelatable lead is curvilinear, such that a given incremental increase in blood lead is associated with an increasingly larger increment of mobilizable lead. The problems associated with this curvilinear relationship in exposure assessment are typified by the recent reports of Saenger et al. (1982) and Piomelli et al. (1984) concerning children and Hansen et al. (1981) concerning adult lead workers. Saenger et al. (1982) noted that significant percentages of children having mild to moderate lead exposure, as discernible by blood lead and EP measurements, had urinary outputs of lead upon challenge with $CaNa_2EDTA$ that qualified them for chelation therapy under CDC guidelines. Similar data were obtained for 210 children evaluated in four medical centers (Piomelli et al., 1984). In adult workers, Hansen et al. (1981) observed that a sizable fraction of subjects with only modest elevations in blood lead levels upon EDTA challenge excreted lead in amounts significantly exceeding the upper end of normal. This discrepancy occurred at blood lead levels of 35 µg/dl and above.

The biological basis for the nonlinearity of the relationship between blood lead and chelatable lead appears, in major part, to be the existence of a sizable pool of lead in bone that is labile to chelation. Evidence pointing to this explanation was summarized in Section 10.3.3. The question of how long any lead in this compartment of bone remains labile to chelation has been addressed by several investigators in studies of both children and adults. The question is relevant to the issue of the usefulness of EDTA challenge in assessing evidence for past lead exposure.

Chisolm et al. (1976) found that a group (N = 55) of adolescent subjects 12-22 years old, who had a clinical history of lead poisoning as young children and whose mean blood lead was 22.1 µg/dl at the time of study, yielded chelatable lead values that placed them on the same regression curve as a second group of young children with current elevations of blood lead. The results with the adolescent subjects did not provide evidence that they might have had a past history of lead poisoning. According to the authors, this failure to detect prior exposure suggests that chelatable lead at the time of excessive exposure was not retained in a pool that remained labile to chelation years later, but underwent subsequent excretion or transfer to the inert compartment of bone. One problem with drawing conclusions from this study is that all of the adolescents apparently had one or more courses of chelation therapy and were removed to housing where re-exposure would be minimal as part of their clinical management after lead poisoning was diagnosed. One must assume that chelation therapy removed a significant portion of the mobile lead burden and that placement in lead-free housing reduced the extent of any further exposure. The obvious question is how this group of adolescents would compare with subjects who had excessive chronic lead exposure as young children but who did not require or receive chelation therapy.

Former lead workers challenged with EDTA show chelatable lead values that are significantly above normal years after workplace exposure ceases (e.g., Alessio et al., 1976; Prêrovskà and Teisinger, 1970). In the case of former lead workers, blood lead also remains elevated, suggesting that the mobile lead pool in bone remains in equilibrium with lead in blood.

The closer correspondence of chelatable lead with actual tissue lead burdens, compared to blood lead, is also reflected in a better correlation of this parameter with such biological indicators of impairment as EP, although this correlation is seen only in adults. Similarly, Alessio et al. (1976) found that EP in former lead workers was more significantly correlated with chelatable lead than with blood lead.

Consideration of both the intake versus blood lead and the blood lead versus chelatable lead curves leads to the prediction that the level of lead exposure per se is more closely related to tissue lead burden than is blood lead. This appears to be the case in experimental animals. Azar et al. (1973) and Grant et al. (1980) reported that levels of lead in brain, kidney, and femur followed more of a direct proportionality with the level of dosing than with blood lead. These observations may relate to the fact that plasma lead rises proportionately faster than whole blood lead.

Finally, there is the question of how adequately an internal indicator such as blood lead reflects changes in tissue burden when exposure changes abruptly. In the study of Björklund et al. (1981), lead levels in both blood and brain were monitored over a 6-week period in rats exposed to lead through their drinking water. Blood lead rose rapidly by day 1, during which time brain lead content was only slightly elevated. After day 1, the rate of increase in blood lead began to taper off, while brain lead began to rise in a nearly linear fashion up to the end of the experiment. From day 7 to 21, blood lead increased from approximately 45 to 55 µg/dl, while brain lead increased approximately twofold.

Abrupt reduction in exposure similarly appears to be associated with a more rapid response in blood than in soft tissues, particularly brain. Goldstein and Diamond (1974) reported that termination of intravenous administration of lead to 30-day-old rats resulted in a sevenfold drop of lead in blood by day 7. At the same time, brain lead levels did not decrease significantly. A similar difference in brain and blood response was reported by Momcilović and Kostial (1974).

In all of the above studies, blood lead was of limited value in reflecting changes in the brain, which is the significant target organ for lead exposure in children. With abrupt increases in exposure level, the problem concerns a much more rapid approach to steady state in blood than in brain. Conversely, the biological half-time for lead clearance from blood in the young rats of both the Goldstein and Diamond (1974) and Momcilović and Kostial (1974) studies was much less than it appeared to be for lead movement from brain.

Despite the limitations in indexing tissue burden and exposure changes, blood lead remains the one readily accessible measure that can demonstrate in a relative way the relationship of various effects to increases in exposure.

10.7 METABOLISM OF LEAD ALKYLS

The lower alkyl lead compounds used as gasoline additives, tetraethyl lead (TEL) and tetramethyl lead (TML), are much more neurotoxic on an equivalent dose basis than inorganic lead. These agents are emitted in auto exhaust, and their rate of environmental degradation depends on such factors as sunlight, temperature, and ozone levels. There is also some concern that organolead compounds may result from biomethylation in the environment (see Chapter 6). Finally, a problem arises with the practice among children of sniffing leaded gasoline. The available information dealing with metabolism of lead alkyls is derived mainly from experimental animal studies, studies of workers exposed to the agents, and cases of lead alkyl poisoning.

10.7.1 Absorption of Lead Alkyls in Humans and Animals

The respiratory intake and absorption of TEL and TML in the vapor state was investigated by Heard et al. (1979), who used human volunteers inhaling ^{203}Pb-labeled TEL and TML. Initial lung deposition rates were 37 and 51 percent for TEL and TML, respectively. Of these amounts, 40 percent of TEL was lost by exhalation within 48 hr, while the corresponding figure for TML within 48 hr was 20 percent. The remaining fraction was absorbed. The effect of gasoline vapor on these parameters was not investigated. In an earlier study Mortensen (1942) reported that adult rats inhaling TEL labeled with ^{203}Pb (0.07-7.00 mg TEL/l) absorbed 16-23 percent of the fraction reaching the alveoli. Gasoline vapor had no effect on the absorption rates.

Respiratory absorption of organolead bound to particulate matter has not been specifically studied as such. According to Harrison and Laxen (1978), neither TEL nor TML adheres to particulate matter to any significant extent, but the toxicologically equivalent trialkyl derivatives, formed from photolytic dissociation or ozonolysis in the atmosphere, may do so.

10.7.1.1 Gastrointestinal Absorption. Information on the rate of absorption of lead alkyls through the GI tract is not available in the literature. Given the level of gastric acidity (pH 1.0) in humans, one would expect TML and TEL to be rapidly converted to the corresponding trialkyl forms, which are comparatively more stable (Bade and Huber, 1970). Given the similarity of the chemical and biochemical behavior of trialkyl leads to their Group IV analogs, the trialkyltins, the report of Barnes and Stoner (1958) that triethyltin is quantitatively absorbed from the GI tract indicates that triethyl and trimethyl lead would be extensively absorbed via this route.

10.7.1.2 Percutaneous Absorption of Lead Alkyls.

In contrast to inorganic lead salts, both TEL and TML are rapidly and extensively absorbed through the skin in rabbits and rats (Kehoe and Thamann, 1931; Laug and Kunze, 1948), and lethal effects can be rapidly induced in these animals by merely exposing the skin. Laug and Kunze (1948) observed that systemic uptake of TEL was still 6.5 percent even after most of the TEL had evaporated from the skin surface. The rate of passage of TML was somewhat slower than that of TEL in the study of Davis et al. (1963). Absorption of either agent was retarded somewhat when applied in gasoline.

10.7.2 Biotransformation and Tissue Distribution of Lead Alkyls

To understand the *in vivo* fate of lead alkyls, one must first discuss the biotransformation processes of lead alkyls known to occur in mammalian systems. Tetraethyl and tetramethyl lead both undergo oxidative dealkylation in mammals to the triethyl or trimethyl metabolites, which are now accepted as the actual toxic forms of these alkyls.

Studies of the biochemical mechanisms for these transformations, as noted by Kimmel et al. (1977), indicate a dealkylation mediated by a P-450 dependent mono-oxygenase system in liver microsomes, with intermediate hydroxylation. In addition to rats (Cremer, 1959; Stevens et al., 1960; Bolanowska, 1968), mice (Hayakawa, 1972), and rabbits (Bolanowska and Garczyński, 1968), this transformation also occurs in humans accidentally poisoned with TEL (Bolanowska et al., 1967) or workers chronically exposed to TEL (Adamiak-Ziemba and Bolanowska, 1970).

The rate of hepatic oxidative de-ethylation of TEL in mammals appears to be rather rapid; Cremer (1959) reported a maximum hourly conversion rate of approximately 200 μg TEL/g rat liver. In comparison with TEL, TML may undergo transformation at either a slower rate (in rats) or more rapidly (in mice), according to Cremer and Callaway (1961) and Hayakawa (1972).

Other transformation steps involve conversion of triethyl lead to the diethyl form, the process appearing to be species-dependent. Bolanowska (1968) did not report the formation of diethyl lead in rats, while significant amounts of it are present in the urine of rabbits (Arai et al., 1981) and humans (Chiesura, 1970). Inorganic lead is formed in various species treated with TEL, whether the TEL arises from degradation of the diethyl lead metabolite or from some other direct process (Bolanowska, 1968). Degradation appears to occur in rats, since little or no diethyl lead is found, whereas significant amounts of inorganic lead are present. Formation of inorganic lead with lead alkyl exposure may account for the hematological effects seen in humans chronically exposed to the lead alkyls (see Chapter 12, Section 12.3), including children who inhale leaded gasoline vapor.

Partitioning of triethyl or trimethyl lead, the corresponding neurotoxic metabolites of TEL and TML, between the erythrocyte and plasma appears to be species-dependent. Byington et al. (1980) studied the partitioning of triethyl lead between cells and plasma *in vitro* using washed human and rat erythrocytes and found that human cells had a very low affinity for the alkyl lead while rat cells bound the alkyl lead in the globin moiety at a ratio of three molecules per hemoglobin tetramer. Similarly, injected triethyl lead was found to be associated with whole blood levels approximately 10-fold greater than in rat plasma. The available literature on TEL poisoning in humans concurs; significant plasma lead values have been routinely reported (Boeckx et al., 1977; Goldings and Stewart, 1982). These data indicate that the rat is a poor model for studying the adverse effects of lead alkyls in human subjects.

The biological half-life in blood for the lead alkyls depends on whether clearance of the tetraalkyl or trialkyl forms is being observed. Heard et al. (1979) found that ^{203}Pb-labeled TML and TEL inhaled by human volunteers was rapidly cleared from the blood (by 10 hr), followed by a reappearance of lead. The fraction of lead in plasma initially was quite high, approximately 0.7, suggesting the presence of tetra/trialkyl lead. However, the subsequent rise in blood lead showed all of it essentially present in the cell, which would indicate inorganic or possibly diethyl lead. Triethyl lead in rabbits was more rapidly cleared from the blood (3-5 days) than was the trimethyl form (15 days) when administered as such (Hayakawa, 1972).

Tissue distribution of lead in both humans and animals exposed to TEL and TML primarily involves the trialkyl metabolites. Levels are highest in liver, followed by kidney, then brain (Bolanowska et al., 1967; Grandjean and Nielsen, 1979). Nielsen et al. (1978) observed measurable amounts of trialkyl lead in samples of brain tissue from subjects with no known occupational exposure.

The available studies on tissue retention of triethyl or trimethyl lead provide variable findings. Bolanowska (1968) noted that tissue levels of triethyl lead in rats were almost constant for 16 days after a single injection of TEL. Hayakawa (1972) found that the half-life of triethyl lead in brain was 7-8 days for rats. The half-time for trimethyl lead was much longer. In humans, Yamamura et al. (1975) reported two tissue compartments for triethyl lead having half-lives of 35 and 100 days (Yamamura et al., 1975).

10.7.3 Excretion of Lead Alkyls

The renal tract is the main route of lead excretion in various species exposed to lead alkyls (Grandjean and Nielsen, 1979). The chemical forms of lead in urine suggest that the differing amounts of the various forms are species-dependent. Arai et al. (1981) found that rabbits given TEL parenterally excreted lead primarily in the form of diethyl lead (69 percent) and inorganic lead (27 percent), triethyl lead accounting for only 4 percent. Bolanowska and Garczyński (1968) found that triethyl lead levels were somewhat higher in the urine of rats than in that of rabbits. In humans, Chiesura (1970) found that trialkyl lead was never greater than 9 percent of total lead content in workers with heavy TEL exposure.

Adamiak-Ziemba and Bolanowska (1970) reported similar data; the fraction of triethyl lead in the urine was approximately 10 percent of total lead.

The urinary rates of lead excretion in human subjects with known levels of TEL exposure were also reported by Adamiak-Ziemba and Bolanowska (1970). In workers involved with the blending and testing of leaded gasoline, workplace air levels of lead (as TEL) ranged from 0.037 to 0.289 mg/m^3 and the corresponding urine lead levels ranged from 14 to 49 μg/l, of which approximately 10 percent was triethyl lead.

10.8 SUMMARY

Toxicokinetic parameters of lead absorption, distribution, retention, and excretion relating external environmental lead exposure to various adverse effects have been discussed in this chapter. Also considered were various influences on these parameters, e.g., nutritional status, age, and stage of development. A number of specific issues in lead metabolism by animals and humans were addressed, including:

1. How does the developing organism from gestation to maturity differ from the adult in toxicokinetic response to lead intake?
2. What do these differences in lead metabolism portend for relative risk for adverse effects?
3. What are the factors that significantly change the toxicokinetic parameters in ways relevant to assessing health risk?
4. How do the various interrelationships among body compartments for lead translate to assessment of internal exposure and changes in internal exposure?

10.8.1 Lead Absorption in Humans and Animals

The amounts of lead entering the bloodstream via various routes of absorption are influenced not only by the levels of the element in a given medium but also by various physical and chemical parameters and specific host factors, such as age and nutritional status.

10.8.1.1 Respiratory Absorption of Lead. The movement of lead from ambient air to the bloodstream is a two-part process: deposition of some fraction of inhaled air lead in the deeper part of the respiratory tract and absorption of the deposited fraction. For adult humans, the deposition rate of particulate airborne lead as likely encountered by the general population is around 30-50 percent, with these rates being modified by such factors as particle size and ventilation rates. All of the lead deposited in the lower respiratory tract appears to be absorbed, so that the overall absorption rate is governed by the deposition rate, i.e., approximately 30-50 percent. Autopsy results showing no lead accumulation in the lung indicate total absorption of deposited lead.

All of the available data for lead uptake via the respiratory tract in humans have been obtained with adults. Respiratory uptake of lead in children, while not fully quantifiable, appears to be comparatively greater on a body-weight basis. A second factor influencing the relative deposition rate in children is airway dimensions. One report has estimated that the 10-year-old child has a deposition rate 1.6- to 2.7-fold higher than the adult on a weight basis.

The chemical form of the lead compound inhaled does not appear to be a major determinant of the extent of alveolar absorption of lead. While experimental animal data for quantitative assessment of lead deposition and absorption for the lung and upper respiratory tract are limited, available information from the rat, rabbit, dog, and nonhuman primate support the findings that respired lead in humans is extensively and rapidly absorbed. Over the range of air lead encountered by the general population, absorption rate does not appear to depend on air lead level.

10.8.1.2 Gastrointestinal Absorption of Lead. Gastrointestinal (GI) absorption of lead mainly involves lead uptake from food and beverages as well as lead deposited in the upper respiratory tract and eventually swallowed. It also includes ingestion of non-food material, primarily in children via normal mouthing activity and pica. Two issues of concern with lead uptake from the gut are the comparative rates of such absorption in developing versus adult organisms, including humans, and how the relative bioavailability of lead affects such uptake.

By use of metabolic balance and isotopic (radioisotope or stable isotope) studies, various laboratories have provided estimates of lead absorption in the human adult on the order of 10-15 percent. This rate can be significantly increased under fasting conditions to 45 percent, compared to lead ingested with food. The latter figure also suggests that beverage lead is absorbed to a greater degree since much beverage ingestion occurs between meals.

The relationship of the chemical/biochemical form of lead in the gut to absorption rate has been studied, although interpretation is complicated by the relatively small amounts given and the presence of various components in food already present in the gut. In general, however, chemical forms of lead and their incorporation into biological matrices seem to have a minimal impact on lead absorption in the human gut. Several studies have focused on the question of differences in GI absorption rates for lead between children and adults. Such rates for children are considerably higher than for adults: 10-15 percent for adults versus approximately 50 percent for children. Available data for the absorption of lead from nonfood items such as dust and dirt on hands are limited, but one study has estimated a figure of 30 percent. For paint chips, a value of about 17 percent has been estimated.

Experimental animal studies show that, like humans, the adult animal absorbs much less lead from the gut than the developing animal. Adult rats maintained on ordinary rat chow absorb 1 percent or less of the dietary lead. Various animal species studies make it clear that the newborn absorbs a much greater amount of lead than the adult, supporting studies showing this age dependency in humans. Compared to an absorption rate of about 1 percent in adult rats, the rat pup has a rate 40-50 times greater. Part, but not most, of the difference can be ascribed to a difference in dietary composition. In nonhuman primates, infant monkeys absorb 65-85 percent of lead from the gut, compared to 4 percent for the adults.

The bioavailability of lead in the GI tract as a factor in its absorption has been the focus of a number of experimental studies. These data show the following: (1) lead in a number of forms is absorbed about equally, except for lead sulfide; (2) lead in dirt and dust and in different chemical forms is absorbed at about the same rate as pure lead salts added to a diet; (3) lead in paint chips undergoes significant uptake from the gut; and (4) in some cases, physical size of particulate lead can affect the rate of GI absorption. In humans, GI absorption rate of lead appears to be independent of quantity in the gut up to a level of at least 400 μg. In animals, dietary levels between 10 and 100 ppm result in reduced absorption.

10.8.1.3 Percutaneous Absorption of Lead. Absorption of inorganic lead compounds through the skin is of much less significance than absorption through respiratory and GI routes. In contrast, absorption through skin is far more significant than through other routes for the lead alkyls (see Section 10.7.1.2). One recent study using human volunteers and ^{203}Pb-labeled lead acetate showed that under normal conditions, skin absorption of lead alkyls approached 0.06 percent.

10.8.1.4 Transplacental Transfer of Lead. Lead uptake by the human and animal fetus readily occurs, such transfer going on by the 12th week of gestation in humans, and increasing throughout fetal development. Cord blood contains significant amounts of lead, correlating with, but somewhat lower than, maternal blood lead levels. Evidence for such transfer, besides the measured lead content of cord blood, includes fetal tissue analyses and reduction in maternal blood lead during pregnancy. There also appears to be a seasonal effect on the fetus, summer-born children showing a trend to higher blood lead levels than those born in the spring.

10.8.2 Distribution of Lead in Humans and Animals

In this subsection, the distributional characteristics of lead in various portions of the body (blood, soft tissue, calcified tissue, and the "chelatable" or potentially toxic body burden) are discussed as a function of such variables as exposure history and age.

10.8.2.1 Lead in Blood. More than 99 percent of blood lead is associated with the erythrocytes in humans under steady-state conditions, but it is the very small fraction transported in plasma and extracellular fluid that provides lead to the various body organs. Most (∿50 percent) erythrocyte lead is bound within the cell, primarily associated with hemoglobin (particularly HbA_2), with approximately 5 percent bound to a 10,000-dalton fraction, 20 percent to a heavier molecule, and 25 percent to lower-weight species. Several studies with lead workers and patients indicate that the fraction of lead in plasma versus whole blood increases above ~50-60 μg/dl blood lead.

Whole blood lead in daily equilibrium with other compartments in adult humans appears to have a biological half-life of 25-28 days and comprises about 1.9 mg in total lead content, based on isotope studies. Other data from lead-exposed workers indicate that half-life depends on mobile lead burden. Human blood lead responds rather quickly to abrupt changes in exposure. With increased lead intake, blood lead achieves a new value in approximately 40-60 days, while a decrease in exposure may be associated with variable new blood values, depending upon the exposure history. This dependence presumably reflects lead resorption from bone. With age, furthermore, a moderate increase occurs in blood lead during adulthood. Levels of lead in blood of children tend to show a peak at 2-3 years of age (probably caused by mouthing activity), followed by a decline. In older children and adults, levels of lead are sex-related, females showing lower levels than males even at comparable levels of exposure.

In plasma, lead is virtually all bound to albumin and only trace amounts to high-weight globulins. Which binding form constitutes an "active" fraction for movement to tissues is impossible to state. The most recent studies of the erythrocyte/plasma relationship in humans indicate an equilibrium between these blood compartments, such that levels in plasma rise with levels in whole blood in fixed proportion up to approximately 50-60 μg/dl, whereupon the relationship becomes curvilinear.

10.8.2.2 Lead Levels in Tissues. Of necessity, various relationships of tissue lead to exposure and toxicity in humans must generally be obtained from autopsy samples. Limitations on these data include questions of how such samples represent lead behavior in the living population, particularly with reference to prolonged illness and disease states. The adequate characterization of exposure for victims of fatal accidents is a problem, as is the fact that such studies are cross-sectional in nature, with different age groups assumed to have had similar exposure in the past.

10.8.2.2.1 Soft tissues. After age 20 most soft tissues (in contrast to bone) in humans do not show age-related changes. Kidney cortex shows an increase in lead with age, which may be associated with the formation of nuclear inclusion bodies. Absence of lead accumulation in most soft tissues results from a turnover rate for lead similar to that in blood.

Based on several autopsy studies, soft-tissue lead content for individuals not occupationally exposed is generally below 0.5 μg/g wet weight, with higher values for aorta and kidney cortex. Brain tissue lead level is generally below 0.2 μg/g wet weight with no change with increasing age, although the cross-sectional nature of these data would make changes in low brain lead levels difficult to discern. Autopsy data for both children and adults indicate that lead is selectively accumulated in the hippocampus, a finding that is also consistent with the regional distribution in experimental animals.

Comparisons of lead levels in soft-tissue autopsy samples from children with results from adults indicate that such values are lower in infants than in older children, while children aged 1-16 years had levels comparable to those for adult women. In one study, lead content of brain regions did not materially differ for infants and older children compared to adults. Complicating these data somewhat are changes in tissue mass with age, although such changes are less than for the skeletal system.

Subcellular distribution of lead in soft tissue is not uniform. High amounts of lead are sequestered in the mitochondria and nucleus of the cell. Nuclear accumulation is consistent with the existence of lead-containing nuclear inclusions in various species, and a large body of data demonstrate the sensitivity of mitochondria to injury by lead.

10.8.2.2.2 Mineralizing tissue. Lead becomes localized and accumulates in human calcified tissues, i.e., bones and teeth. This accumulation in humans begins with fetal development and continues to approximately 60 years of age. The extent of lead accumulation in bone ranges up to 200 mg in men ages 60-70 years, while in women lower values have been measured. Based upon various studies, approximately 95 percent of total body lead is lodged in the bones of human adults, with uptake distributed over trabecular and compact bone. In the human adult, bone lead is both the most inert and the largest body pool, and accumulation can serve to maintain elevated blood lead levels years after exposure, particularly occupational exposure, has ended.

By comparison to human adults, only 73 percent of body lead is lodged in the bones of children, which is consistent with other information that the skeletal system of children is more metabolically active than that of adults. Furthermore, bone tissue in children is less dense than in adults. While the increase in bone lead level across childhood is modest, about twofold if expressed as concentration, the total accumulation rate is actually 80-fold, taking into account a 40-fold increase in skeletal mass. To the extent that some significant fraction of total bone lead in children and adults is relatively labile, in terms of health risk for the whole organism it is more appropriate to consider the total accumulation rather than just changes in concentration.

The traditional view that the skeletal system was a "total" sink for body lead (and by implication a biological safety feature to permit significant exposure in industrialized populations) never did agree with even older information on bone physiology, e.g., bone remodeling. This view is now giving way to the idea that there are at least several bone compartments for lead, with different mobility profiles. Bone lead, then, may be more of an insidious source of long-term internal exposure than a sink for the element. This aspect of the issue is summarized more fully in the next section. Available information from studies of uranium miners and human volunteers who ingested stable isotopes indicates that there is a relatively inert bone compartment for lead, having a half-life of several decades, as well as a rather labile compartment that permits an equilibrium between bone and tissue lead.

Tooth lead also increases with age at a rate proportional to exposure and roughly proportional to blood lead in humans and experimental animals. Dentine lead is perhaps the most responsive component of teeth to lead exposure since it is laid down from the time of eruption until shedding. This characteristic underlies the usefulness of dentine lead levels in assessing long-term exposure.

10.8.2.2.3 Chelatable lead. Mobile lead in organs and systems is potentially more active toxicologically in terms of being available to biological sites of action. Hence, this fraction of total body lead burden is a more significant predictor of imminent toxicity. In reality, direct measurement of such a fraction in human subjects would not be possible. In this regard, chelatable lead, measured as the extent of plumburesis in response to administration of a chelating agent, specifically $CaNa_2EDTA$, is now viewed as the most useful probe of undue body burden in children and adults.

A quantitative description of the inputs to the body lead fraction that is chelant-mobilizable is difficult to define fully, but it most likely includes a labile lead compartment within bone as well as within soft tissues. Support for this view includes the following: (1) the age-dependency of chelatable lead, but not lead in blood or soft tissues; (2) evidence of removal of bone lead in chelation studies with experimental animals; (3) *in vitro* studies of lead mobilization in bone organ explants under closely defined conditions; (4) tracer-modeling estimates in human subjects; and (5) the complex nonlinear relationship of blood lead and lead intake through various media. Data for children and adults showing a logarithmic relationship of chelatable lead to blood lead and the phenomenon of "rebound" in blood lead elevation after chelation therapy regimens (without obvious external re-exposure) offer further support.

10.8.2.2.4 Animal studies. Animal studies have helped to sort out some of the relationships of lead exposure to *in vivo* distribution of the element, particularly the impact of skeletal lead on whole body retention. In rats, lead administration results in an initial increase of lead levels in soft tissues, followed by loss of lead from soft tissue via excretion and transfer to bone. Lead distribution appears to be relatively independent of dose. Other studies have shown that lead loss from organs follows first-order kinetics except for loss from bone, and that the skeletal system in rats and mice is the kinetically rate-limiting step in whole-body lead clearance.

The neonatal animal seems to retain proportionally higher levels of tissue lead compared to the adult and manifests slow decay of brain lead levels while showing a significant decline over time in other tissues. This decay appears to result from enhanced lead entry to the brain because of a poorly developed brain barrier system as well as from enhanced body retention of lead by young animals.

The effects of such changes as metabolic stress and nutritional status on body redistribution of lead have been noted. Lactating mice, for example, are known to demonstrate tissue redistribution of lead, specifically bone-lead resorption with subsequent transfer of both lead and calcium from mother to pups.

10.8.3 Lead Excretion and Retention in Humans and Animals

10.8.3.1 Human Studies. Dietary lead in humans and animals that is not absorbed passes through the GI tract and is eliminated with feces, as is the fraction of air lead that is swallowed and not absorbed. Lead entering the bloodstream and not retained is excreted through the renal and GI tracts, the latter via biliary clearance. The amounts excreted through these routes are a function of such factors as species, age, and exposure characteristics.

Based upon the human metabolic balance data and isotope excretion findings of various investigators, short-term lead excretion in adult humans amounts to 50-60 percent of the absorbed fraction, with the balance moving primarily to bone and some fraction (approximately half) of this stored amount eventually being excreted. This estimated overall retention figure of 25 percent necessarily assumes that isotope clearance reflects that for body lead in all compartments. The rapidly excreted fraction has a biological half-life of 20-25 days, similar to that for lead removal from blood, based on isotope data. This similarity indicates a steady rate of lead clearance from the body. In terms of partitioning of excreted lead between urine and bile, one study indicates that the biliary clearance is about 50 percent that of renal clearance.

Lead accumulates in the human body with age, mainly in bone, up to around 60 years of age, when a decrease occurs with changes in intake as well as in bone mineral metabolism. As noted earlier, the total amount of lead in long-term retention can approach 200 mg, and even much higher in the case of occupational exposure. This rate corresponds to a lifetime average retention rate of 9-10 μg Pb/day. Within shorter time frames, however, retention will vary considerably because of such factors as development, disruption in the individuals' equilibrium with lead intake, and the onset of such states as osteoporosis.

The age-dependency of lead retention/excretion in humans has not been well studied, but most of the available information indicates that children, particularly infants, retain a significantly higher amount of lead than adults. While autopsy data indicate that pediatric subjects at isolated points in time actually have a lower fraction of body lead lodged in bone, which probably relates to the less dense bones of children as well as high bone mineral turnover, a full understanding of longer-term retention over childhood must consider the exponential growth rate occurring in children's skeletal systems over the time period for which bone lead concentrations have been gathered. This parameter itself represents a 40-fold mass increase. This significant skeletal growth rate has an impact on an obvious question: if children take in more lead on a body-weight basis than adults, absorb and retain more lead than adults, and show only modest elevations in blood lead compared to adults in the face of a more active skeletal system, where does the lead go? A second factor is the assumption that blood lead in children relates to body lead burden in the same quantitative fashion as in adults, an assumption that remains to be proven adequately.

10.8.3.2 Animal Studies. In rats and other experimental animals, both urinary and fecal excretion appear to be important routes of lead removal from the organism. The relative partitioning between the two modes is species- and dose-dependent. With regard to species differences, biliary clearance of lead in the dog is but 2 percent of that for the rat, while such excretion in the rabbit is 50 percent that of the rat.

Lead movement from laboratory animals to their offspring via milk constituents is a route of excretion for the mother as well as a route of exposure for the young. Comparative studies of lead retention in developing versus adult animals such as rats, mice, and nonhuman primates make it clear that retention is significantly greater in the young animal. These observations support those studies showing greater lead retention in children. Some recent data indicate that a differential retention of lead in young rats persists into the post-weaning period, calculated as either uniform dosing or uniform exposure.

10.8.4 Interactions of Lead with Essential Metals and Other Factors

Toxic elements such as lead are affected in their toxicokinetic or toxicological behavior by interactions with a variety of biochemical factors, particularly nutrients.

10.8.4.1 Human Studies. In humans, the interactive behavior of lead and various nutritional factors is expressed most significantly in young children, with such interactions occurring against a backdrop of rather widespread deficiencies in a number of nutritional components. Various surveys have indicated that iron, calcium, zinc, and vitamin deficiencies are widespread among the pediatric population, particularly the poor. A number of reports have documented the association of lead absorption with suboptimal nutritional states for iron and calcium, reduced intake being associated with increased lead absorption.

10.8.4.2 Animal Studies. Reports of lead-nutrient interactions in experimental animals have generally described such relationships for a single nutrient, using relative absorption or tissue retention in the animal to index the effect. Most of the recent data are for calcium, iron, phosphorus, and vitamin D. Many studies have established that diminished dietary calcium is associated with increased blood and soft-tissue lead content in such diverse species as the rat, pig, horse, sheep, and domestic fowl. The increased body burden of lead arises from both increased GI absorption and increased retention, indicating that the lead-calcium interaction operates at both the gut wall and within body compartments. Lead appears to traverse the gut via both passive and active transfer. It involves transport proteins normally operating for calcium transport, but is taken up at the site of phosphorus, not calcium, absorption.

Iron deficiency is associated with an increase of lead in tissues and increased toxicity, effects that are expressed at the level of lead uptake by the gut wall. In vitro studies indicate an interaction through receptor-binding competition at a common site, which probably involves iron-binding proteins. Similarly, dietary phosphate deficiency enhances the extent of lead retention and toxicity via increased uptake of lead at the gut wall, both lead and phosphate being absorbed at the same site in the small intestine. Results of various studies of the resorption of phosphate along with lead have not been able to identify conclusively a mechanism for the elevation of tissue lead. Since calcium plus phosphate retards lead absorption to a greater degree than simply the sums of the interactions, an insoluble complex of all these elements may be the basis of this retardation.

Unlike the inverse relationship existing for calcium, iron, and phosphate versus lead uptake, vitamin D levels appear directly related to the rate of lead absorption from the GI tract, since the vitamin stimulates the same region of the duodenum where lead is absorbed. A number of other nutrient factors are known to have an interactive relationship with lead:

1. Increases in dietary lipids increase the extent of lead absorption, with the extent of the increase being highest with polyunsaturates and lowest with saturated fats, e.g., tristearin.
2. The interactive relationship of lead and dietary protein is not clear cut, and either suboptimal or excess protein intake will increase lead absorption.
3. Certain milk components, particularly lactose, greatly enhance lead absorption in the nursing animal.
4. Zinc deficiency promotes lead absorption, as does reduced dietary copper.

Taken collectively, human and animal data dealing with the interaction of lead and nutrients indicate that there are heterogeneous subsets of the human population. In terms of pedatric population risk for lead exposure, children having multiple nutrient deficiencies are in the highest exposure risk category.

10.8.5 Interrelationships of Lead Exposure with Exposure Indicators and Tissue Lead Burdens

Three issues involving lead toxicokinetics evolve toward a full connection between lead exposure and its adverse effects: (1) the temporal characteristics of internal indices of lead exposure; (2) the biological aspects of the relationship of lead in various media to various indicators in internal exposure; and (3) the relationship of various internal indicators of exposure to target tissue lead burdens.

10.8.5.1 Temporal Characteristics of Internal Indicators of Lead Exposure. The biological half-life for newly absorbed lead in blood may be as short as weeks, or several months. Or, it may be longer, depending on the mobile lead burden in the body. Compared to mineral tissues, this medium reflects relatively recent exposure. If recent exposure is fairly representative of exposure over a considerable period of time, e.g., exposure of lead workers, then blood lead is more useful than for cases where exposure is intermittent or different across time, as in the case of lead exposure of children. Accessible mineralized tissue, such as shed teeth, extend the time frame back to years of exposure, since teeth accumulate lead with age and as a function of the extent of exposure. Such measurements are, however, retrospective in nature, in that identification of excessive exposure occurs after the fact and thus limits the possibility of timely medical intervention, exposure abatement, or regulatory policy concerned with ongoing control strategies.

Perhaps the most practical solution to the dilemma posed by both tooth and blood lead analyses is *in situ* measurement of lead in teeth or bone during the time when active accumulation occurs, e.g., 2- to 3-year-old children. Available data using X-ray fluorescence analysis do suggest that such approaches are feasible and can be reconciled with such issues as acceptable radiation hazard risk to subjects.

10.8.5.2 Biological Aspects of External Exposure/Internal Indicator Relationships. The literature indicates clearly that the relationship of lead in relevant media for human exposure to blood lead is curvilinear when viewed over a relatively broad range of blood lead values. This curvilinearity implies that the unit change in blood lead per unit intake of lead in some medium varies across this range of exposure, with comparatively smaller blood lead changes occurring as internal exposure increases.

Given our present knowledge, such a relationship cannot be taken to mean that body uptake of lead is proportionately lower at higher exposure, because it may simply mean that blood lead becomes an increasingly unreliable measure of target-tissue lead burden with increasing exposure. While the basis of the curvilinear relationship remains to be identified, available animal data suggest that it may be related to the increasing fraction of blood lead in plasma as blood lead increases above approximately 50-60 μg/dl.

10.8.5.3 Internal Indicator/Tissue Lead Relationships. In living human subjects, direct determination of tissue lead burdens or how these relate to adverse effects in target tissues is not possible. Some accessible indicator (e.g., lead in a medium such as blood or a biochemical surrogate of lead such as erythrocyte protoporphyrin), must be employed. While blood lead still remains the only practical measure of excessive lead exposure and health risk, evidence continues to accumulate that such an index has some limitations in either reflecting tissue lead burdens or changes in such tissues with changes in exposure.

At present, the measurement of plumburesis associated with challenge by a single dose of a lead-chelating agent such as $CaNa_2EDTA$ is considered the best indicator of the mobile, potentially toxic fraction of body lead. Chelatable lead is logarithmically related to blood lead, such that an incremental increase in blood lead is associated with an increasingly larger increment of mobilizable lead. The problems associated with this logarithmic relationship may be seen in studies of children and lead workers in whom moderate elevation in blood lead levels can disguise levels of mobile body lead. In one recent multi-institution study of 210 children, for example, 12 percent of children with blood lead 30-39 µg/dl, and 38 percent with levels of 40-49 µg/dl, had a positive EDTA-challenge response and required further evaluation or treatment. At blood lead levels such as these, the margin of protection against severe intoxication is reduced. The biological basis of the logarithmic chelatable lead/blood lead relationship rests, in large measure, with the existence of a sizeable bone lead compartment that is mobile enough to undergo chelation removal and, hence, potentially mobile enough to move into target tissues.

Studies of the relative mobility of chelatable lead over time indicate that, in former lead workers, removal from exposure leads to a protracted washing out of lead (from bone resorption of lead) to blood and tissues, with preservation of a bone burden amenable to subsequent chelation. Studies with children are inconclusive, since the one investigation directed to this end employed pediatric subjects who all underwent chelation therapy during periods of severe lead poisoning. Animal studies demonstrate that changes in blood lead with increasing exposure do not agree with tissue uptake in a time-concordant fashion, nor does decrease in blood lead with reduced exposure signal a similar decrease in target tissue, particularly in the brain of the developing organism.

10.8.6 Metabolism of Lead Alkyls

The lower alkyl lead components used as gasoline additives, tetraethyl lead (TEL) and tetramethyl lead (TML), may themselves poise a toxic risk to humans. In particular, there is among children a problem of sniffing leaded gasoline.

10.8.6.1 Absorption of Lead Alkyls in Humans and Animals. Human volunteers inhaling labeled TEL and TML show lung deposition rates for the lead alkyls of 37 and 51 percent, respectively, values which are similar to those for particulate inorganic lead. Significant portions of these deposited amounts were eventually absorbed. Respiratory absorption of organolead bound to particulate matter has not been specifically studied as such.

While specific data for the GI absorption of lead alkyls in humans and animals are not available, their close similarity to organotin compounds, which are quantitatively absorbed, would argue for extensive GI absorption. In contrast to inorganic lead salts, the lower lead alkyls are extensively absorbed through the skin and animal data show lethal effects with percutaneous uptake as the sole route of exposure.

10.8.6.2 Biotransformation and Tissue Distribution of Lead Alkyls. The lower lead alkyls TEL and TML undergo monodealkylation in the liver of mammalian species via the P-450-dependent mono-oxygenase enzyme system. Such transformation is very rapid. Further transformation involves conversion to the dialkyl and inorganic lead forms, the latter accounting for the effects on heme biosynthesis and erythropoiesis observed in alkyl lead intoxication. Alkyl lead is rapidly cleared from blood and shows a higher partitioning into plasma than inorganic lead, with triethyl lead clearance being more rapid than that of the methyl analog.

Tissue distribution of alkyl lead in humans and animals primarily involves the trialkyl metabolites. Levels are highest in liver, followed by kidney, then brain. Of interest is the fact that there are detectable amounts of trialkyl lead from autopsy samples of human brain even in the absence of occupational exposure. In humans, there appear to be two tissue compartments for triethyl lead, having half-times of 35 and 100 days.

10.8.6.3 Excretion of Lead Alkyls. With alkyl lead exposure, excretion of lead through the renal tract is the main route of elimination. The chemical forms being excreted appear to be species-dependent. In humans, trialkyl lead in workers chronically exposed to alkyl lead is a minor component of urine lead, approximately 9 percent.

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11. ASSESSMENT OF LEAD EXPOSURES AND ABSORPTION IN HUMAN POPULATIONS

11.1 INTRODUCTION

This chapter describes effects on internal body burdens of lead in human populations resulting from exposure to lead in their environment. Particular attention is paid to changes in indices of internal lead exposure that follow changes in external lead exposures. Blood lead is the main index of internal lead exposure discussed here, although other indices, such as levels of lead in teeth and bone, are also briefly discussed.

The following terms and definitions are used in this chapter. Sources of lead are those components of the environment (e.g., gasoline combustion, smelters) from which significant quantities of lead are released into various environmental media of exposure. Environmental media are routes by which humans become exposed to lead (e.g., air, soil, food, water, dust). External exposures are levels at which lead is present in any or all of the environmental media. Internal exposures are amounts of lead present in various body tissues and fluids.

The present chapter is structured to achieve the following four main objectives:

(1) Elucidation of patterns of internal lead exposures in U.S. populations and identification of important demographic covariates.

(2) Characterization of relationships between external and internal exposures to lead by exposure medium (air, food, water or dust).

(3) Identification of specific sources of lead which result in increased internal exposure levels.

(4) Estimation of the relative contributions of various sources of lead in the environment to total internal exposure as indexed by blood lead level.

The existing scientific literature must be examined in light of the investigators' own objectives and the quality of the scientific investigations performed. Although all studies need to be evaluated in regard to their methodology, the more quantitative studies are evaluated here in greater depth. A discussion of the main types of methodological points considered in such evaluations is presented in Section 11.2.

Patterns of internal exposure to lead in human populations are discussed in Section 11.3. This begins with a brief examination of the historical record of internal lead exposure in human populations. These data serve as a backdrop against which recent U.S. levels can be contrasted and define the relative magnitude of external lead exposures in the past and present. The contrast is structured as follows: historical data, recent data from populations thought to be isolated from urbanized cultures, and then U.S. populations showing various degrees of urbanization and industrialization.

The statistical treatment of distributions of blood lead levels in human populations is the next topic discussed. As part of that discussion, the empirical characteristics of blood lead distributions in well-defined homogeneous populations are denoted. Important issues addressed include the proper choice of estimators of central tendency and dispersion, estimators of percentile values and the potential influence of errors in measurement on statistical estimation involving blood lead data.

Then recent patterns of internal exposure in U.S. and other populations showing change in blood lead levels are discussed in detail. Estimates of internal lead exposure and identification of demographic covariates are made. Studies examining the recent past for evidence of change in internal exposure levels are presented. Next is an examination of extensive evidence which points towards gasoline lead being an important determinant of changes in blood lead level associated with exposures to airborne lead of populations in the United States and elsewhere.

Section 11.4 focuses on general relationships between external exposures and levels of internal exposure. The distribution of lead in man is diagramatically depicted by the component model shown in Figure 11-1. Of particular importance for this document is the relationship between lead in air and lead in blood. If lead in air were the only medium of exposure, then the interpretation of a statistical relationship between lead in air and lead in blood would be relatively simple. However, this is not the case. Lead is present in a number of environmental media, as described in Chapter 7 and summarized in Figure 11-1. There are relationships between lead levels in air and lead concentrations in food, soil, dust, and water. As shown in Chapters 6, 7, and 8, lead emitted into the atmosphere ultimately comes back to contaminate the earth. However, only limited data are currently available that provide a quantitative estimate of the magnitude of this secondary lead exposure. The implication is that an analysis involving estimated lead levels in all environmental media may tend to underestimate the relationship between lead in blood and lead in air.

The discussion of relationships between external exposure and internal absorption commences with air lead exposures. Both experimental and epidemiological studies are discussed. Several studies are identified as being of greatest importance in determining the quantitative relationship between lead in blood and lead in air. The form of the relationship between blood lead and air lead is of particular interest and importance. After discussion of air lead versus blood lead relationships, the chapter next discusses the relationship of blood lead to atmospheric lead found in other environmental media. Section 11.5 describes studies of specific lead exposure situations useful in identifying specific environmental sources of lead that contribute to elevated body burdens of lead. The chapter concludes with a summary of key information and conclusions derived from the scientific evidence reviewed.

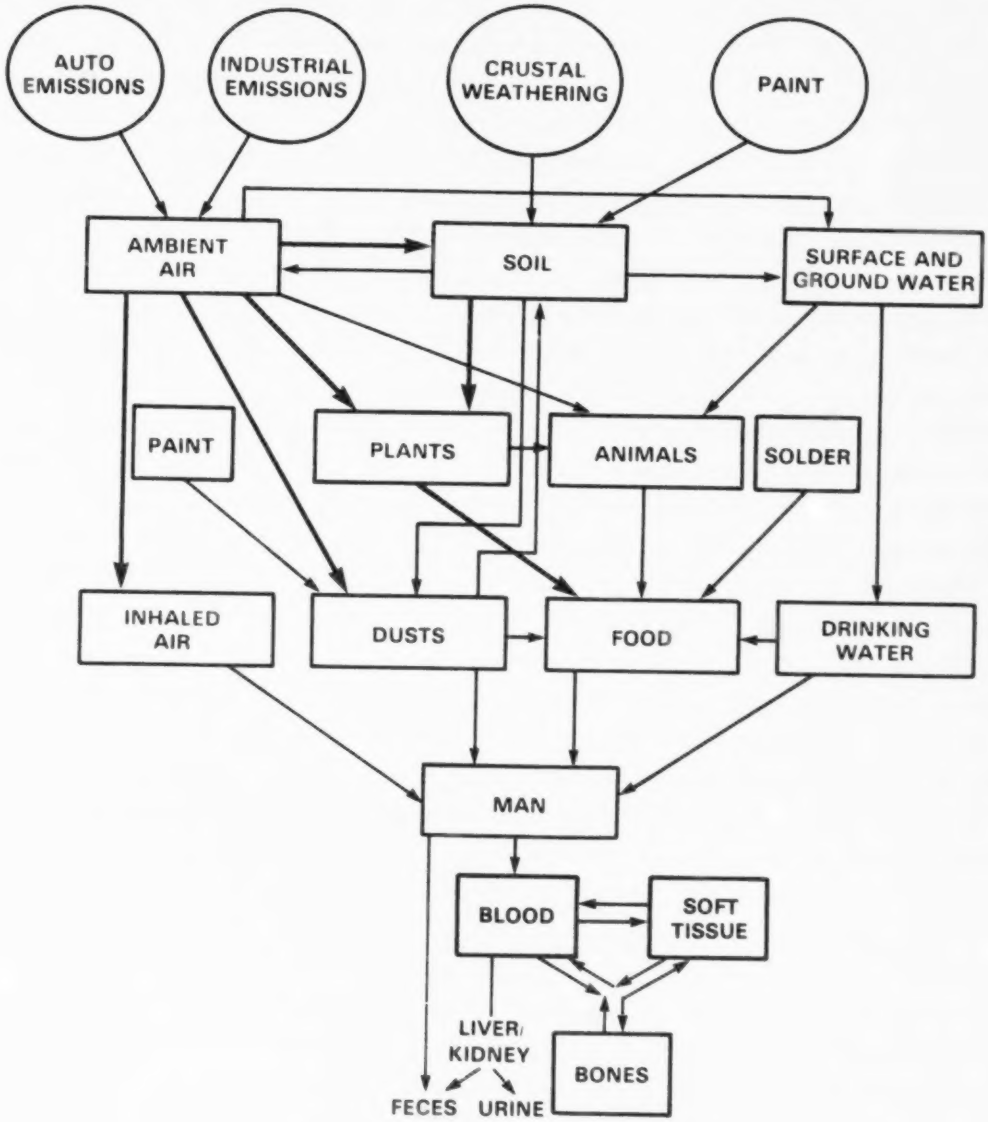


Figure 11-1. Pathways of lead from the environment to and within man.

11.2 METHODOLOGICAL CONSIDERATIONS

11.2.1 Analytical Problems

Internal lead exposure levels in human populations have been estimated by analyses of a variety of biological tissue matrices (e.g., blood, teeth, bone, and hair). Lead levels in each of these matrices have particular biological meanings with regard to external exposure status; these relationships are discussed in Chapter 10. The principal internal exposure index discussed in this chapter is blood lead concentration. Blood lead concentrations are most reflective of recent exposure to lead and bear a consistent relationship to levels of lead in the external environment if the latter have been stable. Blood lead levels are variously reported as μg/100 g, μg/100 ml, μg/dl, ppm, ppb, and μmol/l. The first four measures are roughly equivalent, whereas ppb values are simply divisible by 1000 to be equivalent. Actually there is a small, but not meaningful, difference in blood lead levels reported on a per volume versus per weight difference. The difference results from the density of blood being slightly greater than 1 g/ml. For the purposes of this chapter, data reported on a weight or volume basis are considered equal. On the other hand, blood lead data reported on a μmol/l basis must be multiplied by 20.72 to get the equivalent μg/dl value. Data reported originally as μmol/l in studies reviewed here are converted to μg/dl in this chapter.

As discussed in Chapter 9, the measurement of lead in blood has been accomplished via a succession of analytical procedures over the years. The first reliable analytical methods available were wet chemistry procedures, succeeded by increasingly automated instrumental procedures. With these changes in technology there has been increasing recognition of the importance of controlling for contamination in the sampling and analytical procedures. These advances, as well as institution of external quality control programs, have resulted in markedly improved analytical results. Data summarized in Chapter 9 show that a generalized improvement in analytical results across many laboratories occurred during Federal Fiscal Years 1977-1979. No further marked improvement was seen during Federal Fiscal Years 1979-1981.

Because of interest in being able to attribute specific proportions of blood lead as coming from specific environmental sources, isotopic lead determinations in blood have become an important analytic technique. As difficult as it is to determine blood lead levels accurately, the achievement of accurate lead isotopic determinations is even more difficult. Experience gained from the isotopic lead experiment (ILE) in Italy (reviewed in detail in Section 11.3.6.2.1) has indicated that extremely aggressive quality control and contamination control programs must be implemented to achieve acceptable results. With proper procedures, meaningful differences on the order of a single nanogram are achievable.

11.2.2 Statistical Approaches

Many studies have summarized the distribution of lead levels in humans. These studies usually report measures of central tendency (means) and dispersion (variances). In this chapter, the term "mean" refers to the arithmetic mean unless stated otherwise. This measure is always an estimate of the average value, but it estimates the center of the distribution (50th percentile) only for symmetric distributions. Many authors provide geometric means, which estimate the center of the distribution if the distribution is lognormal. Geometric means are influenced less by unusually large values than are arithmetic means. A complete discussion of the lognormal distribution is given by Aitchison and Brown (1966), including formulas for converting from arithmetic to geometric means.

Most studies also give sample variances or standard deviations in addition to the means. If geometric means are given, then the corresponding measure of dispersion is the geometric standard deviation. Aitchison and Brown (1966) give formulas for the geometric standard deviation and, also, explain how to estimate percentiles and construct confidence intervals. All of the measures of dispersion actually include three sources of variation: population variation, measurement variation, and variation due to sampling error. Values for these components are needed in order to evaluate a study correctly. There are also sources of variation related to the inclusion of predictive variables in the model, or their exclusion. Such variables include different lead uptakes attributable to exposure to lead in dust, soil, food, water, paint in deteriorated housing, and other pathways. If included in the model, the remaining sources of variation are due to unmeasured differences in intrinsic metabolism and behavior. It has been the general goal in this chapter to include all attributable sources of variation, thus reducing the estimates of variability to biological differences, uncertainties in exposure, and measurement variations that cannot be further attributed. We recognize that if only air lead exposure is controlled, then there will be additional variation in blood lead response due to imperfectly controlled covariation of lead exposure from related pathways. This additional variation can be dealt with in practice by use of a larger geometric standard deviation.

A separate issue is the form of the distribution of blood lead values. Although the normal and lognormal distributions are commonly used, there are many other possible distributions. The form is important for two reasons: 1) it determines which is more appropriate, the arithmetic or geometric mean, and 2) it determines estimates of the fraction of a population exceeding given internal lead levels under various external exposures. Both of these questions arise in the discussion of the distribution of human blood lead levels and are of importance, ultimately, for deriving a rationale for standard-setting purposes.

11.2.3 Confounding of Relevant Variables

Failure to include relevant variables is the most serious difficulty in evaluating studies on lead in human populations. This usually occurs when the blood lead response is wholly attributed to some observed variable, e.g., the lead concentration in air, dust, or water. Typical confounders for air lead include the following: (1) inhalation exposures not captured by stationary air lead monitors, particularly those that occur from personal exposure to leaded gasoline or its combustion products; (2) noninhalation exposures to air lead not captured by stationary monitors, e.g., ingestion of food products contaminated by lead fallout, leaded dust, and soil; (3) ingestion of lead in water and food that is inadvertantly associated with air lead exposure. Socioeconomic factors may be important here also. See Brunekreef (1984) and Snee (1982b,c) for additional comments.

Air lead concentrations are typically highest in urban centers where the concentration of motor vehicles is greatest. (Communities with lead smelters are an exception). Suburban and rural areas have much lower air lead concentrations. However, suburban and rural residents may spend more time in motor vehicles due to longer trips to work, school, and shopping. There is some reason to believe that higher lead concentrations may be found near and inside automobiles (see Spengler et al., (1984), Section 11.3.6.2.1), thus offsetting the decreased ambient air lead concentrations measured by stationary monitors in non-urban areas. Unfortunately, there is no way at this time to separate the response to average ambient air lead levels from variations in personal lead exposure patterns.

Children are known to ingest quantities of dust and soil by normal hand-mouth contact. In studies in which dust lead concentrations or hand lead quantities are measured, their contribution is very large -- usually much larger than the lead intake by direct inhalation. In smelter communities all of these variables -- ambient air lead, dust lead, soil lead, and lead on children's hands -- are likely to be high. It may then be difficult to separate the contributions of each of these components, and if any one is not measured, then its influence on blood lead may be attributed to the other variables. This may cause little difficulty when in fact there is a single source for all exposure pathways, but positive confounding may cause difficulty in extrapolating the relationship to situations in which air and dust lead are less strongly coupled. Similarly, the particle size distribution may change with distance from the source (smelter, highway, etc.) and particle size is known to affect the fraction of lead absorbed by the lungs. However, air and dust lead concentrations also decrease with distance from the source, thus leading to potential confounding of concentration and size effects. This may be a factor in some smelter studies, e.g., the Silver Valley, Idaho, study discussed later.

Socioeconomic status (SES), sex, age, and race are also confounded with air lead. Lower SES populations tend to be found in areas with high air lead concentration such as urban centers and smelter communities. There may also be systematic SES differences in use of lead-soldered food and beverage cans and in exposure to food products with high lead content and in personal and household cleanliness, as well. The latter is important because dust control can substantially reduce blood lead burdens in children (Charney et al., 1983). Lower SES is also associated with older housing stocks and increasing risk of encountering lead paint in poor condition and lead pipes in water systems. Lower SES is also more likely to be associated with inadequate dietary calcium, iron, and vitamins, all of which increase lead absorption and the likely toxic effects of any given level of lead exposure. In addition, lower SES is also more likely to imply reduced awareness of lead hazards and reduced resources for dealing with such hazards. Other factors, such as the presence of pets in a household and the amount of time spent playing outside, are not obviously related to SES.

Males have higher blood lead levels than females, at least beyond ages 10-11. The most plausible explanations suggest differential exposure, with older boys and men typically spending more time in contact with motor vehicles, in jobs with potential lead exposure, and more often outdoors. The risk factors have not been fully identified. Black children also often have higher blood leads than do white children, even after adjusting for SES and other covariates; the reason for this difference has also not been clarified, but may be related to positive confounding factors.

For modelling purposes, the appropriate geometric standard deviation removes a portion of the total variation in blood lead due to differences in air lead exposure without removing the variance due to these other factors. Controlling for race, urbanization, age, income, and location may overcontrol in this case, since it may remove variance due to environmental exposure factors that will remain after air lead is controlled to any given level. It may thus be prudent and conservative to compensate for this overcontrol by increasing the geometric standard deviation when only air lead is used as a predictor variable.

All of the above factors make it difficult to analyze adequately such a highly confounded environmental exposure variable as air lead. However, there appear to be enough studies in which several of the possible confounding factors were also measured that it is possible to obtain reasonable estimates of blood lead changes in response to differences in concentrations of lead in air, dust, soil, water, and diet, seasonal variations, and personal risk factors such as household quality, occupational exposure, and motor vehicle exposure. The remaining sections of this chapter discuss studies from which such estimates are derived. Experimental studies are much less subject to confounding, and where available, are generally preferred. Unfortunately, experimental studies do not provide information about total environmental air lead exposure, which includes multiple exposure pathways and possible time lags of many years due to passage of lead through the soil, the food chain, and water supplies. It is thus also necessary to obtain information about total air lead exposure from observational studies. All observational studies suffer confounding problems. This chapter focuses mainly on those observational studies in which a substantial number of the probable important confounding factors are either measured or are controlled by the design of the study. Less importance is assigned to those studies in which too many important covariates have been omitted, or which otherwise seem critically deficient.

11.3 LEAD IN HUMAN POPULATIONS

11.3.1 Introduction

This descriptive section presents information on dimensions of current internal exposures to lead for United States populations. Several aspects of the current situation regarding internal lead exposures are addressed. First, attention is focused on showing how current indices of internal exposure compare with indices derived from historical samples. Also, the question of how contemporaneous populations compare with one another with respect to internal exposures is addressed. The primary data involved in this discussion are blood lead levels from populations showing varying degrees of urbanization. Blood lead levels are lowest in populations living remotely from urban influences and increase as one goes from rural to urban areas, suggesting that higher blood lead levels are linked to urban lifestyles. Following this discussion, data are presented on several large studies in the United States and a large worldwide study. These data address two principal questions: 1) are there identifiable subpopulations in the United States which exhibit higher than average blood lead levels, and 2) how do United States blood lead levels compare with other countries? This section next presents studies which examine recent time trends in blood lead levels in the United States and elsewhere, and then concludes with a discussion of evidence which points towards gasoline lead being an important determinant of changes in blood lead levels associated with exposures to airborne lead of populations in the United States and elsewhere.

11.3.2 Ancient and Remote Populations

One question of much interest in understanding environmental pollutants is the extent to which current ambient exposures exceed background levels. Because lead is a naturally occurring element it can be surmised that some level has been and will always be present in the human body; the question of interest is what is the difference between body burdens of current subgroups of the United States population and those "natural" levels. Information regarding this issue has been developed from studies of populations that lived in the past and populations that currently live in remote areas far from the influence of industrial and urban lead exposures.

Man has used lead since antiquity for a variety of purposes. These uses have afforded the opportunity for some segments of the human population to be exposed to lead and subsequently absorb it into the body. Because lead accumulates over a lifetime in bones and teeth and because bones and teeth stay intact for extremely long times, it is possible to estimate the extent to which populations in the past have been exposed to lead. Because of the problems of scarcity of samples and little knowledge of how representative the samples are of conditions at the time, the data from these studies provide only rough estimates of the extent of absorption. Further complicating the interpretation of these data are debates over proper analytical procedures and the question of whether skeletons and teeth pick up or release lead from or to the soil in which they are interred (Waldron et al., 1979; Waldron, 1981).

Waldron et al. (1979) have argued that any lead found in ancient bones probably is an accurate reflection of exposure during life. They reported a small study which showed no correlation between bone and soil lead concentrations. Later, however, Waldron (1981) reported a study in which the postmortem bone lead levels appeared to be much too high to have been developed during life. The bones were recovered from lead coffins. Electron microprobe analysis on one bone from a lead coffin showed that the lead was concentrated on the surfaces of the bone. This suggested that the lead in bones came from the lead coffin and led Waldron (1981) to suggest that "in any further study of the lead content of bones from archaeological sites, steps must be taken to assess environmental lead levels and if these are unusually high, the results of the analyses should be viewed with suspicion." Barry and Connolly (1981) express further concern over the use of paleontological remains as doubtful criteria for the *in vivo* assessment of lead exposure in past populations.

Despite these methodological difficulties, several studies provide data by which to estimate internal exposure patterns among ancient populations, and some studies have included data from both past and current populations for comparisons. Data from specific studies of bone and teeth in ancient populations are summarized below in Section 11.3.2.1. In contrast to the study of ancient populations using bone and teeth lead levels, several studies have looked at the issue of lead contamination from the perspective of comparing blood lead levels in current remote and urbanized populations. These studies using blood lead levels as an indicator found mean blood concentrations in remote populations between 1 and 5 μg/dl (an order of magnitude below current U.S. urban population means), as discussed in Section 11.3.2.2 below.

11.3.2.1 Ancient Populations. Table 11-1 summarizes several studies that analyzed bones and teeth to yield approximate estimates of lead absorption in the past. Some of these studies also analyzed contemporary current samples so that a comparison between past and present could be made. Studies summarized in Table 11-1 show an increase of lead levels in bone and teeth from older to contemporary samples.

Samples from the Sudan (ancient Nubians) were collected from several different archaeological periods (Grandjean et al., 1979). The oldest sample (3300-2900 B.C.) averaged 0.6 μg/g for bone and 0.9 μg/g for teeth. Data from the later time of 1650-1350 B.C. show a substantial increase in absorbed lead. Comparison of even the most recent ancient samples with a current Danish sample showed a four- to eightfold increase over time.

The Shapiro et al. (1975) study compared the tooth lead content of ancient populations with that of current remote populations and, also, with current urban populations. The ancient Egyptian samples (1st and 2nd millenia) exhibited the lowest tooth lead levels, with a mean of 9.7 μg/g. The more recent Peruvian Indian samples (12th century) had similar levels (13.6 μg/g). The contemporary Alaskan Eskimo samples had a mean of 56.0 μg/g, while Philadelphia samples had a mean of 188.3 μg/g. These data suggest an increasing pattern of lead absorption from ancient populations to current remote and urban populations.

Data have also been obtained from ancient Peruvian and Pennsylvanian samples (Becker et al., 1968). The Peruvian and Pennsylvanian samples for American Indian populations were from approximately the same era (~1200-1400 A.D.). Little lead was used in these cultures as reflected by chemical analysis of bone lead content. The values were less than 5 μg/g for both samples. In contrast, values obtained for modern samples from residents of Syracuse, New York, ranged from 5 to 110 μg/g. Ericson et al. (1979) also analyzed bone speciments from ancient Peruvians. Samples from 4500-3000 years ago to about 1400 years ago were reasonably constant (<0.2 μg/g).

Fosse and Wesenberg (1981) reported a study of Norwegian teeth samples from several eras. The older material from 1200-1800 A.D. was significantly lower in lead (1.22 to 1.81 μg/g) than modern samples (3.73 to 4.12 μg/g).

Aufderheide et al. (1981) report a study of 16 skeletons from colonial America. Two social groups, identified as plantation proprietors and laborers, had distinctly different exposures to lead as shown by the analyses of the skeletal samples. The proprietor group averaged 185 μg/g bone ash while the laborer group averaged 35 μg/g.

Changes in bone and tooth lead concentrations over time (as determined by the above or other studies) have been evaluated by Angle and McIntire (1982), as graphically depicted in Figure 11-2. Lead concentrations in human bones apparently markedly increased among ancient

TABLE 11-1. SUMMARY OF REPRESENTATIVE STUDIES OF PAST EXPOSURES TO LEAD

Population studied	Age of sample	Method of analysis	Lead levels, μg/g dry weight Bone	Lead levels, μg/g dry weight Tooth
Nubians[1] vs. Modern Danes	3300 B.C. to 750 A.D. (5000 yrs. old)	FASS, ASV		
Nubians				
A-group	3300 to 2900 B.C.	FASS, ASV	0.6†	0.9*
C-group	2000 to 1600 B.C.	FASS, ASV	1.0†	2.1*
Pharonic	1650 to 1350 B.C.	FASS, ASV	2.0†	5.0*
Merotic, X-group and Christians	1 to 750 A.D.	FASS, ASV	1.2†	3.2*
Danes	Contemporary	FASS, ASV	5.5†	25.7*
Ancient Peruvians[2]	500-600 yrs. old	Arc emission spectroscopy	<5††	
Ancient Pennsylvanian Indians	500 yrs. old	Arc emission spectrosocpy	N.D.	
Recent Syracuse, NY	Contemporary	Arc emission spectroscopy	5-110††	
Uvdal[3]	Buried from before 1200 A.D. to 1804	AAS		1.22**
Modern Buskend County	Contemporary	AAS		4.12**
Bryggen	Medieval Bergen	AAS		1.81**
Norway	Contemporary	AAS		3.73**
Ancient Egyptian[4]	1st and 2nd millennia			
Peruvian Indian	12th century	ASV		9.7
Alaskan Eskimo	Contemporary	ASV		13.6
Philadelphian	Contemporary	ASV		56.0
		ASV		188.3

[1] Grandjean et al. (1979).
[2] Becker et al. (1968).
[3] Fosse and Wesenberg (1981).
[4] Shapiro et al. (1975).
*Circumpulpal dentine.
†Temporal bone.
††Tibia/femur.
**Whole tooth, but values corrected for enamel and dentine.

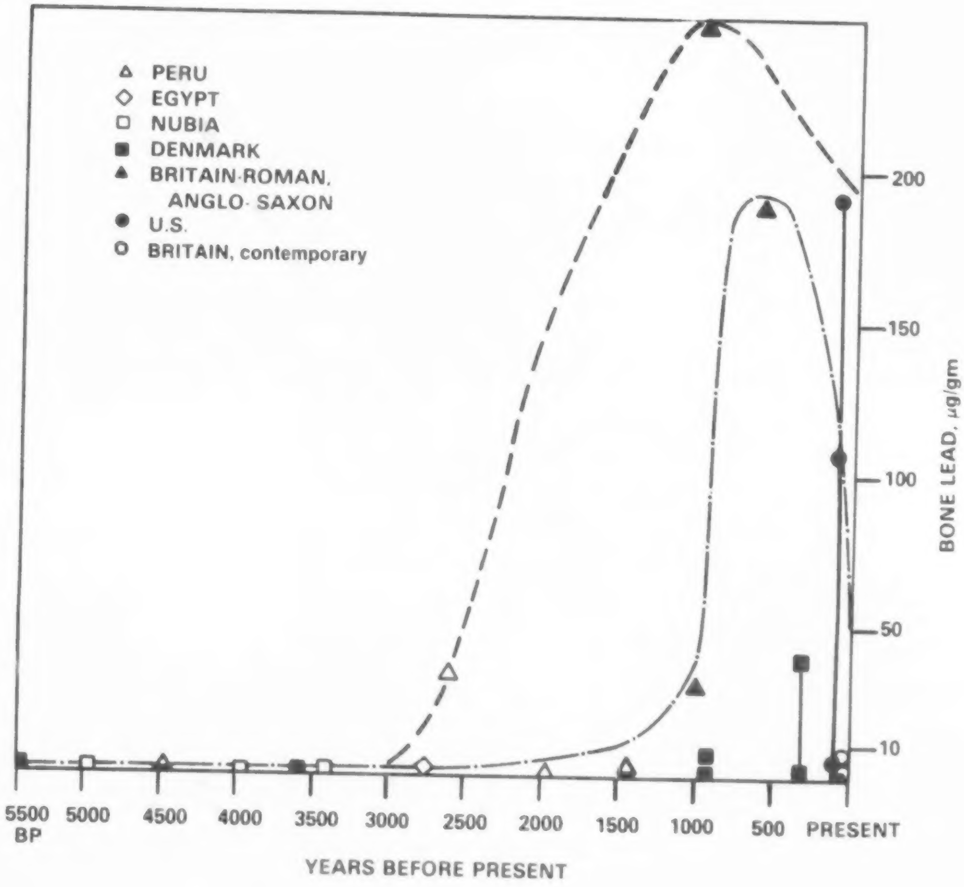


Figure 11-2. Estimated lead concentrations in bones (μg/g) from 5500 years before present (BP) to the present time, from ancient Peru (Ericson et al. 1979) and Egypt, Nubia, and Denmark (Grandjean et al. 1979), Britain in the Roman and Anglo-Saxon (Waldron 1980) eras, contemporary British children (Barry 1981), and U.S. adults in the 1950s (Schroeder and Tipton 1968).

Source: From Angle and McIntire (1982).

------	Early (Britain-Roman, Anglo-Saxon) with soil possibly contaminated with lead.
—·—·—	Early (Britain-Roman, Anglo-Saxon) with soil believed not to be contaminated with lead.
———	Represents range of values.

populations with the introduction of metallurgic processes and dramatic increases in production and utilization of lead. For example, bone lead concentrations consistently below 3 µg/g were found for premetallurgic societies in Peru, Egypt, Nubia, and Denmark, whereas concentrations of lead in bones from England during the early Roman Empire era are reported to be 10-fold higher and to have reached 300 to 400 µg/g by the time of the Norman invasion. The Danish bone lead levels also increased during medieval times and reached peak levels of about 40-50 µg/g in the eighteenth century. The data available for more recent contemporary populations in the twentieth century appear to be widely variable, ranging from 0.1 to 5.4 µg/g reported for contemporary adults in Denmark to 7.5 to 195 µg/g reported for U.S. adults dying in the 1950's. Overall, the available data (despite analytic errors in individual studies) collectively suggest that contemporary Americans, especially urban populations, absorb manifold higher levels of lead than did members of premetallurgic societies.

11.3.2.2 Remote Populations. Several studies have looked at the blood lead levels in current remote populations (Piomelli et al., 1980; Poole et al., 1980). These studies are important in defining baseline levels of internal lead exposures found in the world today.

Piomelli et al. (1980) studied blood lead levels of natives in a remote (far from industrialized regions) section of Nepal. Portable air samplers were used to determine air lead concentrations in the region. The lead content of the air samples proved to be less than the detection limit, 0.004 µg/m^3. A later study by Davidson et al. (1981) found an average air lead concentration of 0.00086 µg/m^3 in remote areas of Nepal, thus confirming the low air lead levels reported by Piomelli et al. (1980).

Blood lead levels reported by Piomelli et al. (1980) for the Nepalese natives were low; the geometric mean blood lead for this population was 3.4 µg/dl. Adult males had a geometric mean of 3.8 µg/dl and adult females, 2.9 µg/dl. Children had a geometric mean blood lead of 3.5 µg/dl. Only 10 of 103 individuals tested had a blood lead level greater than 10 µg/dl. The blood samples, which were collected on filter paper discs, were analyzed by a modification of the Delves cup atomic absorption spectrophotometric method. Stringent quality control procedures were followed for both the blood and air samples. To put these Nepalese values in perspective, Piomelli et al. (1980) reported analyses of blood samples collected and analyzed by the same methods from Manhattan, New York. New York blood leads averaged about 15 µg/dl, fivefold higher than the Nepalese values.

Poole et al. (1980) reported another study of a remote population, using contamination-free micro-blood sampling and chemical analysis techniques. They reported acceptable precision at blood lead concentrations as low as 5 µg/dl, using spectrophotometry. One hundred children were sampled from a remote area of Papua, New Guinea. Almost all of the children came from families engaging in subsistence agriculture. The children ranged from 7 to 10 years and included both sexes. Blood lead levels ranged from 1 to 13 µg/dl with a mean of 5.2. Although the data appear to be somewhat skewed to the right, they are in good agreement with those of Piomelli for Nepalese subjects.

11.3.3 Levels of Lead and Demographic Covariates in U.S. and Other Populations

Several large surveys of blood lead levels give information on the major demographic covariates in U.S. populations (see also sections 7.3.2.2 and 7.3.2.3.) In addition to the obvious covariates of age, sex, race, and urban-rural differences, there is a more subtle effect of seasonality. Children show a strong midsummer peak (hence the characterization of lead poisoning as "the summer disease" (Hunter, 1978)). This peak may be attributed to many causes: 1) gasoline lead consumption and lead concentrations are higher in the summer; 2) many people, especially children, spend more time outside during the summer; 3) more beverages are consumed in the summer, increasing exposure from lead-soldered beverage cans; and 4) other seasonal variations in diet, climate, and health status may affect blood lead levels. Thus, seasonality has an effect on all of the demographic studies. The extent to which these demographic studies adjust for seasonality varies.

11.3.3.1 The NHANES II Study. The National Center for Health Statistics has provided the best currently available picture of blood lead levels among United States residents as part of the second National Health and Nutrition Examination Study (NHANES II) conducted from February, 1976 to February, 1980 (Mahaffey et al., 1982; McDowell et al., 1981; Annest et al., 1982; Annest and Mahaffey, 1984). These are the first national estimates of lead levels in whole blood from a representative sample of the non-institutionalized U.S. civilian population aged 6 months to 74 years.

From a total of 27,801 persons identified through a stratified, multi-stage probability cluster sample of households throughout the United States, blood lead determinations were scheduled for 16,563 persons including all children ages 6 months to 6 years, and one-half of all persons ages 7-74. Sampling was scheduled in 64 sampling areas over the four-year period according to a previously determined itinerary to maximize operational efficiency and response of participants. Because of the constraints of cold weather, the examination trailers traveled in the moderate climate areas during the winter, and the more northern areas during the summer (McDowell et al., 1981).

All reported blood lead levels were based on samples collected by venipuncture. Blood lead levels were determined by atomic absorption spectrophotometry using a modified Delves cup micro-method. Specimens were analyzed in duplicate, with both determinations done independently in the same analytical run. Quality control was maintained by two systems, a bench system and a blind insertion of samples. If the NHANES II replicates differed by more than

7 µg/dl, the analysis was repeated for the specimen (about 0.3 percent were reanalyzed). If the average of the replicate values of either "bench" or "blind" control specimens fell outside previously established 95 percent confidence limits, the entire run was repeated. The estimated coefficient of variation for the "bench" quality control ranged from 7 to 15 percent (Mahaffey et al., 1979).

The reported blood lead levels were based on the average of the replicates. Blood lead levels and related data were reported as population estimates; findings for each person were inflated by the reciprocal of selection probabilities, adjusted to account for persons who were not examined and poststratified by race, sex, and age. The final estimates closely approximate the U.S. Bureau of Census estimates for the civilian non-institutionalized population of the United States as of March 1, 1978, aged 1/2-74 years.

Participation rates varied across age categories; the highest non-response rate (51 percent) was for the youngest age group, 6 months through 5 years. Among medically examined persons, those with missing blood lead values were randomly distributed by race, sex, degree of urbanization, and annual family income. These data are probably the best estimates now available regarding the degree of lead absorption in the general United States population.

Forthofer (1983) has studied the potential effects of non-response bias in the NHANES II survey and found no large biases in the health variables. This was based on the excellent agreement of the NHANES II examined data, which had a 27 percent non-response rate, with the National Health Interview Survey data, which had a 4 percent non-response rate.

The national estimates presented below are based on 9933 persons whose blood lead levels ranged from 2.0 to 66.0 µg/dl. The median blood lead for the entire U.S. population is 13.0 µg/dl. It is readily apparent that blacks have a higher blood lead level than whites (medians for blacks and whites were 15.0 and 13.0 µg/dl, respectively).

Tables 11-2 through 11-4 display the observed distribution of measured blood lead levels by race, sex, and age. The possible influence of measurement error on the percent distribution estimates is discussed in Section 11.3.4. Estimates of mean blood lead levels differ substantially with respect to race, age, and sex. Blacks have higher levels than whites, the 6-month to 5-year group is higher than the older age groups, and men are higher than women. Overall, younger children show only a slight age effect, with 2- to 3-year-olds having slightly higher blood lead levels than older children or adults (see Figure 11-3). In the 6-17 year grouping there is a decreasing trend in lead levels with increasing age. Holding age constant, there are significant race and sex differences; as age increases, the difference between males and females in mean blood lead concentrations increases.

TABLE 11-2. NHANES II BLOOD LEAD LEVELS OF PERSONS 6 MONTHS-74 YEARS, WITH WEIGHTED ARITHMETIC MEAN, STANDARD ERROR OF THE MEAN, WEIGHTED GEOMETRIC MEAN, MEDIAN, AND PERCENT DISTRIBUTION, BY RACE AND AGE, UNITED STATES, 1976-80

Race and age	Estimated population in thousands[a]	Number examined[b]	Blood lead level µg/dl								
			Arith-metic mean	Standard error of the mean	Geometric mean	Median	Percent distribution[c]				
							Less than 10	10-19	20-29	30-39	40+
All races[d]											
All ages	203,554	9,933	13.9	0.24	12.8	13.0	22.1	62.9	13.0	1.6	0.3
6 months-5 years	16,852	2,372	16.0	0.42	14.9	15.0	12.2	63.3	20.5	3.6	0.4
6-17 years	44,964	1,720	12.5	0.30	11.7	12.0	27.6	64.8	7.1	0.5	-
18-74 years	141,728	5,841	14.2	0.25	13.1	13.0	21.2	62.3	14.3	1.8	0.4
White											
All ages	174,528	8,369	13.7	0.24	12.6	13.0	23.3	62.8	12.2	1.5	0.3
6 months-5 years	13,641	1,876	14.9	0.43	14.0	14.0	14.5	67.5	16.1	1.8	0.2
6-17 years	37,530	1,424	12.1	0.30	11.3	11.0	30.4	63.4	5.8	0.4	-
18-74 years	123,357	5,069	14.1	0.25	12.9	13.0	21.9	62.3	13.7	1.8	0.4
Black											
All ages	23,853	1,332	15.7	0.48	14.6	15.0	13.3	63.7	20.0	2.3	0.6
6 months-5 years	2,584	419	20.9	0.61	19.6	20.0	2.5	45.4	39.9	10.2	2.0
6-17 years	6,529	263	14.8	0.53	14.0	14.0	12.8	70.9	15.6	0.7	-
18-74 years	14,740	650	15.5	0.54	14.4	14.0	14.7	62.9	19.6	2.0	0.9

[a] At the midpoint of the survey, March 1, 1978.

[b] With lead determinations from blood specimens drawn by venipuncture.

[c] Numbers may not add up to 100 percent due to rounding.

[d] Includes data for races not shown separately.

TABLE 11-3. NHANES II BLOOD LEAD LEVELS OF MALES 6 MONTHS-74 YEARS, WITH WEIGHTED ARITHMETIC MEAN, STANDARD ERROR OF THE MEAN, WEIGHTED GEOMETRIC MEAN, MEDIAN, AND PERCENT DISTRIBUTION, BY RACE AND AGE, UNITED STATES, 1976-80

			Blood lead level µg/dl								
							Percent distribution[c]				
Race and age	Estimated population in thousands[a]	Number examined[b]	Arith-metic mean	Standard error of the mean	Geometric mean	Median	Less than 10	10-19	20-29	30-39	40+
All races[d]											
All ages	99,062	4,945	16.1	0.26	15.0	15.0	10.4	65.4	20.8	2.8	0.5
6 months-5 years	8,621	1,247	16.3	0.46	15.1	15.0	11.0	63.5	21.2	4.0	0.3
6-17 years	22,887	902	13.6	0.32	12.8	13.0	19.1	70.1	10.2	0.7	-
18-74 years	67,555	2,796	16.8	0.28	15.8	16.0	7.6	64.1	24.2	3.4	0.6
White											
All ages	85,112	4,153	15.8	0.27	14.7	15.0	11.3	66.0	19.6	2.6	0.4
6 months-5 years	6,910	969	15.2	0.46	14.2	14.0	13.0	67.6	17.3	2.0	0.1
6-17 years	19,060	753	13.1	0.33	12.4	13.0	21.4	69.5	8.4	0.7	-
18-74 years	59,142	2,431	16.6	0.29	15.6	16.0	8.1	64.8	23.3	3.3	0.6
Black											
All ages	11,171	664	18.3	0.52	17.3	17.0	4.0	59.6	31.0	4.1	1.3
6 months-5 years	1,307	231	20.7	0.74	19.3	19.0	2.7	48.8	35.1	11.1	2.4
6-17 years	3,272	129	16.0	0.62	15.3	15.0	8.0	69.9	21.1	1.0	-
18-74 years	6,592	304	19.1	0.70	18.1	18.0	2.3	56.4	34.9	4.5	1.8

[a] At the mi[illegible]nt of the survey, March 1, 1978.

[b] With lead determinations from blood specimens drawn by venipuncture.

[c] Numbers may not add to 100 percent due to rounding.

[d] Includes data for races not shown separately.

TABLE 11-4. NHANES II BLOOD LEAD LEVELS OF FEMALES 6 MONTHS-74 YEARS, WITH WEIGHTED ARITHEMETIC MEAN, STANDARD ERROR OF THE MEAN, WEIGHTED GEOMETRIC MEAN, MEDIAN, AND PERCENT DISTRIBUTION, BY RACE AND AGE, UNITED STATES, 1976-80

Race and age	Estimated population in thousands[a]	Number examined[b]	Blood lead level, μg/dl								
							Percent distribution[c]				
			Arith-metic mean	Standard error of the mean	Geometric mean	Median	Less than 10	10-19	20-29	30-39	40+
All races[d]											
All ages	104,492	4,988	11.9	0.23	11.1	11.0	33.3	60.5	5.7	0.4	0.2
6 months-5 years	8,241	1,125	15.8	0.42	14.6	15.0	13.5	63.2	19.8	3.0	0.5
6-17 years	22,077	818	11.4	0.32	10.6	11.0	36.6	59.3	3.9	0.2	-
18-74 years	74,173	3,045	11.8	0.22	11.0	11.0	33.7	60.6	5.2	0.3	0.2
White											
All ages	89,417	4,216	11.7	0.23	10.9	11.0	34.8	59.6	5.0	0.4	0.2
6 months-5 years	6,732	907	14.7	0.44	13.7	14.0	16.1	67.3	14.8	1.6	0.2
6-17 years	18,470	671	11.0	0.31	10.3	11.0	40.0	56.9	2.9	0.2	-
18-74 years	64,215	2,638	11.7	0.23	10.9	11.0	34.6	59.9	5.0	0.4	0.2
Black											
All ages	12,682	668	13.4	0.45	12.6	13.0	21.5	67.3	10.3	0.7	0.1
6 months-5 years	1,277	188	21.0	0.69	19.8	20.0	2.2	41.6	45.3	9.2	1.7
6-17 years	3,256	134	13.6	0.64	12.8	13.0	17.7	71.9	10.0	0.4	-
18-74 years	8,148	346	12.7	0.44	12.0	12.0	24.7	68.1	7.2	-	-

[a] At the midpoint of the survey, March 1, 1978.

[b] With lead determinations from blood specimens drawn by venipuncture.

[c] Numbers may not add to 100 percent due to rounding.

[d] Includes data for races not shown separately.

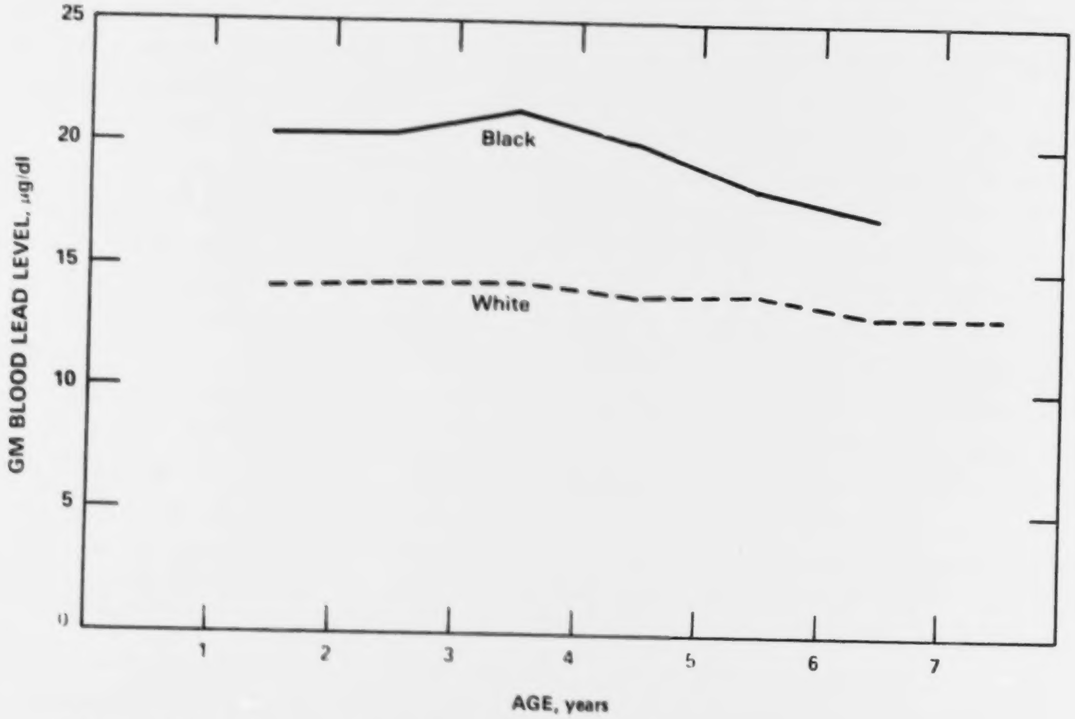


Figure 11-3. Geometric mean blood lead levels by race and age for younger children in the NHANES II study. EPA calculations from data furnished by the National Center for Health Statistics.

Source: Annest and Mahaffey (1984).

For adults 18-74 years, males have greater blood lead levels than females for both whites and blacks. There is a significant relationship between age and blood lead, but it differs for whites and blacks. Whites have increasing blood lead levels until 35-44 years of age and then decline, while blacks have increasing blood lead levels until 55-64.

This study showed a clear relationship between blood lead level and family income group. For both blacks and whites, increasing family income is associated with lower blood lead level. At the highest income level the difference between blacks and whites is the smallest, although blacks still have significantly higher blood lead levels than whites. The racial difference was greatest for the 6-month to 5-year age range.

The NHANES II blood lead data were also examined with respect to the degree of urbanization at the place of residence. The three categories used were urban areas with population greater than one million, urban areas with population less than one million, and rural areas. Geometric mean blood lead levels increased with degree of urbanization for all race-age groups except for blacks 18-74 years of age (see Table 11-5). Most importantly, urban black children aged 6 months - 5 years appeared to have distinctly higher mean blood lead levels than any other population subgroup.

11.3.3.2 The Childhood Blood Lead Screening Programs. In addition to the nationwide picture presented by the NHANES II (Annest et al., 1982) study regarding important demographic correlates of blood lead levels, Billick et al. (1979, 1982) provide large scale analyses of blood lead values from childhood blood lead screening programs in specific cities that also address this issue.

Billick et al. (1979) analyzed data from New York City blood lead screening programs from 1970 through 1976. The data include age in months, sex, race, residence expressed as health district, screening information, and blood lead values expressed in intervals of 10 µg/dl. Only the venous blood lead data (178,588 values), clearly identified as coming from the first screening of a given child, were used. All blood lead determinations were done by the same laboratory. The geometric means of the children's blood lead levels by age, race, and year of collection are presented in Table 11-6. The annual means were calculated from the four quarterly means which were estimated by the method of Hasselblad et al. (1980).

The data obtained for New York are generally consistent with the nationwide results from the NHANES II study. For example, all racial/ethnic groups show an increase in geometric mean blood level with age for the first two years and a general decrease in the older age groups. These age-related patterns are seen in Figure 11-4, which shows the trends for all years (1970-1976) combined. Also, the childhood screening data described by Billick et al. (1979) show higher geometric mean blood lead values for blacks than for Hispanics or for whites. Table 11-6 presents these geometric means for the three racial/ethnic groups for seven years.

TABLE 11-5. WEIGHTED GEOMETRIC MEAN BLOOD LEAD LEVELS FROM NHANES II SURVEY BY DEGREE OF URBANIZATION OF PLACE OF RESIDENCE IN THE U.S. BY AGE AND RACE, UNITED STATES 1976-80 (micrograms/deciliter)

Race and age	Degree of urbanization					
	Urban, ≥1 million		Urban, <1 million		Rural	
All races						
All ages	14.0	(2,395)[a]	12.8	(3,869)	11.9	(3,669)
6 months-5 years	16.8	(544)	15.4	(944)	13.0	(884)
6-17 years	13.1	(414)	11.7	(638)	10.7	(668)
18-74 years - men:	16.9	(677)	15.7	(1,050)	15.1	(1,069)
women:	12.2	(760)	11.0	(1,237)	9.8	(1,048)
Whites						
All ages	14.0	(1,767)	12.5	(3,144)	11.8	(3,458)
6 months-5 years	15.6	(358)	14.4	(699)	12.7	(819)
6-17 years	12.6	(294)	11.4	(510)	10.5	(620)
18-74 years - men:	16.9	(531)	15.4	(889)	14.8	(1,011)
women:	12.4	(584)	10.8	(1,046)	9.8	(1,008)
Blacks						
All ages	14.4	(570)	14.8	(612)	14.4	(150)
6 months-5 years	20.8	(172)	19.2	(205)	16.5	(42)
6-17 years	14.6	(111)	13.6	(113)	13.0	(39)
18-74 years - men:	17.4	(132)	18.6	(134)	18.3	(38)
women:	11.8	(155)	12.4	(160)	11.3	(31)

[a] Number with lead determinations from blood specimens drawn by venipuncture.

Source: Annest and Mahaffey, 1984; Annest et al., 1982.

TABLE 11-6. ANNUAL GEOMETRIC MEAN BLOOD LEAD LEVELS FROM THE NEW YORK BLOOD LEAD SCREENING STUDIES OF BILLICK ET AL. (1979). ANNUAL GEOMETRIC MEANS ARE CALCULATED FROM QUARTERLY GEOMETRIC MEANS ESTIMATED BY THE METHOD OF HASSELBLAD ET AL. (1980)
(micrograms/deciliter)

Ethnic group	Year	Age							
		1-12 mo	13-24 mo	25-36 mo	37-48 mo	49-60 mo	61-72 mo	73- mo	All ages
Black	1970	25.2	28.9	30.1	28.3	27.8	26.4	25.9	27.5
	1971	24.0	29.3	29.9	29.3	28.2	27.2	26.5	27.7
	1972	22.2	26.0	26.3	25.4	24.7	23.9	23.3	24.5
	1973	22.9	26.6	26.0	25.3	24.4	24.1	23.3	24.6
	1974	22.0	25.5	25.4	24.3	23.4	21.8	21.9	23.4
	1975	19.8	22.4	22.4	21.9	21.2	21.4	18.9	21.1
	1976	16.9	20.0	20.6	20.2	19.5	18.2	18.4	19.1
Hispanic	1970	20.8	23.8	24.5	24.7	23.8	23.6	23.0	23.4
	1971	19.9	22.6	24.6	24.4	23.9	23.4	23.5	23.1
	1972	18.7	20.5	21.8	22.2	21.8	21.8	21.0	21.1
	1973	20.2	21.8	22.5	22.8	22.0	21.5	21.7	21.8
	1974	19.8	21.5	22.7	22.5	21.9	20.5	20.2	21.3
	1975	16.3	18.7	19.9	20.1	19.8	19.2	17.2	18.7
	1976	16.0	17.4	18.1	18.2	18.0	16.7	17.2	17.4
White	1970	21.1	25.2	26.0	24.8	26.0	22.6	21.3	23.8
	1971	22.5	22.7	22.7	23.5	21.6	21.3	19.5	21.9
	1972	20.1	21.6	20.7	20.8	21.0	20.2	17.3	20.2
	1973	21.5	21.8	21.7	20.2	21.3	20.7	18.4	20.8
	1974	20.4	21.7	21.3	21.1	20.6	19.5	17.3	20.2
	1975	19.3	17.9	16.1	18.5	16.8	15.4	15.9	17.1
	1976	15.2	18.2	17.1	16.6	16.2	15.9	8.8	15.1

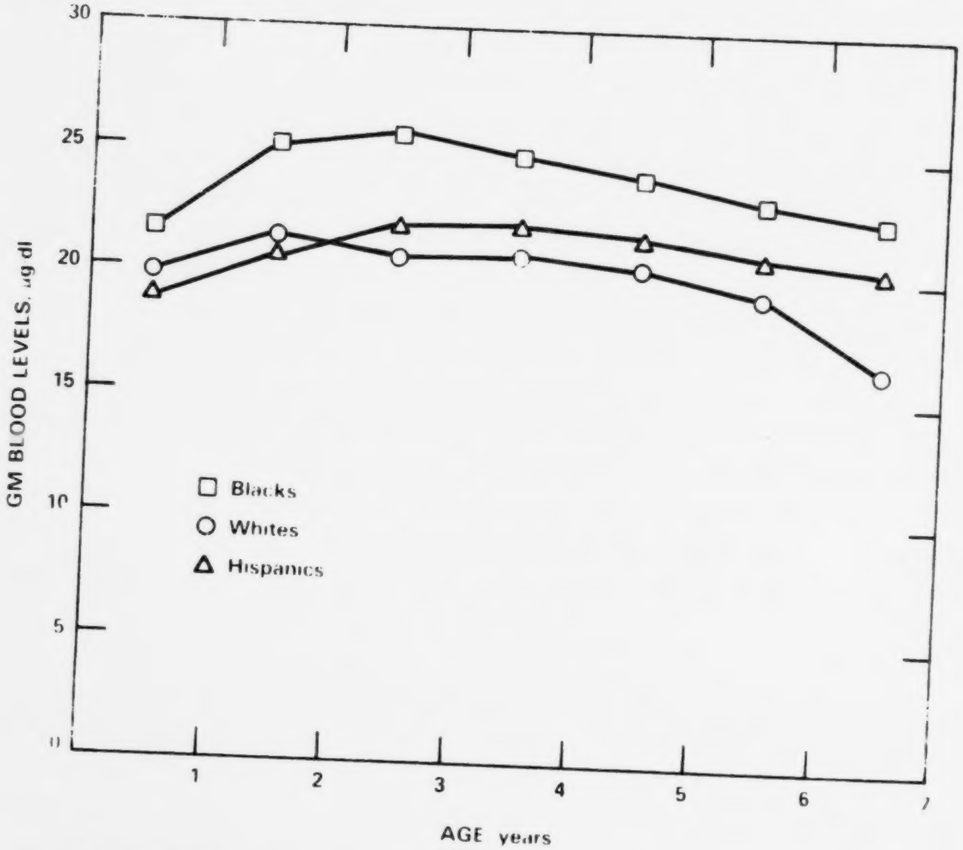


Figure 11-4. Geometric mean blood lead values by race and age for younger children in the New York City screening program (1970-1976).

Source: Adapted from Hasselblad et al. 1980.

Using the method of Hasselblad et al. (1980), the estimated geometric standard deviations were 1.41, 1.42, and 1.42 for blacks, Hispanics, and whites, respectively.

11.3.3.3 Levels of Lead and Demographic Covariates Worldwide. An international study conducted under the auspices of the United Nations Environment Program and the World Health Organization provides the first analytically comparable blood lead data set available to infer the current similarities and differences in lead absorption from country to country (Friberg and Vahter, 1983). Extensive attention was paid to quality control issues, with the resulting blood lead determinations being very comparable from country to country. School teachers were chosen as study subjects since they would be unlikely to have occupational exposures to lead and also because they would have similarities in socioeconomic characteristics. A detailed interview was administered to the subjects to obtain background data.

Figure 11-5, derived from data in the paper, displays the variability from country to country. Unweighted geometric mean blood lead levels ranged from a low of 5.8 µg/dl in Japan to 22.3 µg/dl in Mexico. Teachers in China, Israel, Japan, Sweden, and the United States all had geometric mean blood leads below 8.0 µg/dl.

In general, males showed higher blood lead levels than females; on the average, male teachers had blood lead levels 30 percent higher than females regardless of cigarette smoking status. In most cases cigarette smokers had 10 percent higher blood lead levels than nonsmokers.

11.3.4 Distributional Aspects of Population Blood Lead Levels

The importance of the form of the distribution of blood lead levels was briefly discussed in Section 11.2.2. The distribution form determines which measure of central tendency (arithmetic mean, geometric mean, median) is most appropriate. It is even more important in estimating percentiles in the upper tail of the distribution, an issue of much importance in estimating percentages (or absolute numbers) of individuals in specific population groups likely to be experiencing various lead exposure levels.

Distribution fitting requires large numbers of samples taken from a relatively homogeneous population. A homogeneous population is one in which the distribution of values remains constant when split into subpopulations. These subpopulations could be defined by demographic factors such as race, age, sex, income, degree of urbanization, and degree of exposure. Since these factors always have some effect, a relatively homogeneous population will be defined as one with minimal effects from any factors that contribute to differences in blood lead levels.

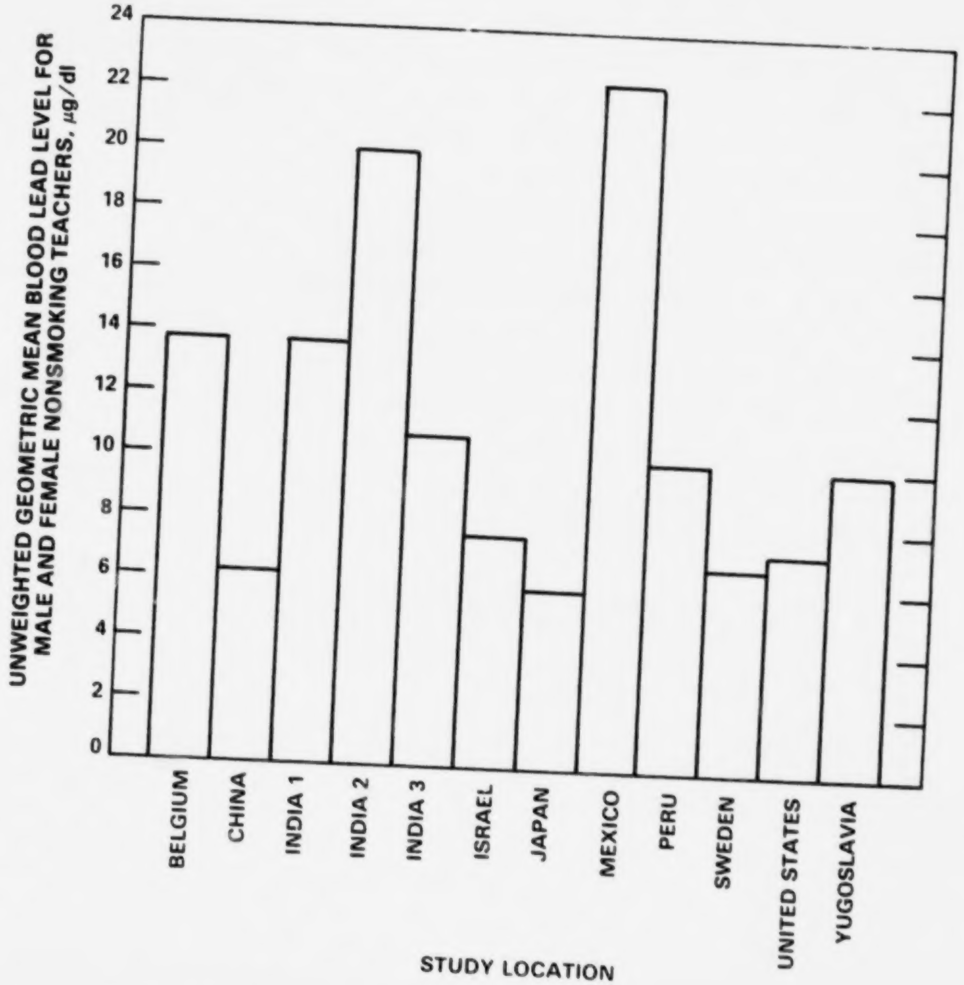


Figure 11-5. Unweighted geometric mean blood lead level for male and female nonsmoking teachers (μg/dl) for several countries.

Source: Derived from Friberg and Vahter (1983).

Several authors have suggested that the distribution of blood lead levels for any relatively homogeneous population closely follows a lognormal distribution (Yankel et al., 1977; Tepper and Levin, 1975; Azar et al., 1975). Lognormality has been noted for other metals, such as ^{90}Sr, ^{144}Ce, Pu, and Ti in various tissues of human populations (Cuddihy et al., 1979; Schubert et al., 1967). Yankel et al. (1977), Tepper and Levin (1975), and Angle and McIntire (1979) all found their blood lead data to be lognormally distributed. Further analysis by EPA of the Houston study of Johnson et al. (1974), the study of Azar et al. (1975), and the New York children screening program reported by Billick et al. (1979) also demonstrated that a lognormal distribution provided a good fit to the data.

The only nationwide survey of blood lead levels in the U.S. population is the NHANES II survey (Annest et al., 1982). In order to obtain a relatively homogeneous subpopulation of lower environmental exposure, the analysis was restricted to whites not living in an SMSA (Standard Metropolitan Statistical Area), with a family income greater than $6,000 per year, the poverty threshold for a family of four at the midpoint of study as determined by the U.S. Bureau of Census. This subpopulation was split into four subgroups based on age and sex. The summary statistics for these subgroups are in Table 11-7.

TABLE 11-7. SUMMARY OF UNWEIGHTED BLOOD LEAD LEVELS IN WHITES NOT LIVING IN AN SMSA, WITH FAMILY INCOME GREATER THAN $6,000

		Unweighted mean					
Subgroup	Sample size	Arith. mean, µg/dl	Geom. mean, µg/dl	Sample median, µg/dl	99th percentile, µg/dl	Arith. std. dev., µg/dl	Geom. std. dev.
Age 1/2 to 6	752	13.7	12.9	13.0	32.0	5.03	1.43
Age 6 to 18	573	11.3	10.6	10.0	24.0	4.34	1.46
Age 18+, men	922	15.7	14.7	15.0	35.8	5.95	1.44
Age 18+, women	927	10.7	10.0	10.0	23.0	4.14	1.46

Each of these four subpopulations were fitted to five different distributions: normal, lognormal, gamma, Weibull, and Wald (Inverse Gaussian) as shown in Table 11-8. Standard chi-square goodness-of-fit tests were computed after collapsing the tails to obtain an expected cell size of five. The goodness-of-fit test and likelihood functions indicate that the lognormal distribution provides a better fit than the normal, gamma, or Weibull. A histogram and the lognormal fit for each of the four subpopulations appear in Figure 11-6.

TABLE 11-8. SUMMARY OF FITS TO NHANES II BLOOD LEAD LEVELS OF WHITES NOT LIVING IN AN SMSA, WITH INCOME GREATER THAN $6,000, FOR FIVE DIFFERENT TWO-PARAMETER DISTRIBUTIONS

Children <6 years

	Chi-square	D.F.*	p-value	log-likelihood	deviation** at 99th percentile
Normal	75.52	8	0.0000	-2280.32	6.61
Lognormal	14.75	10	0.1416	-2210.50	2.57
Gamma	17.51	9	0.0413	-2216.51	4.68
Weibull	66.77	8	0.0000	-2271.57	5.51
Wald	15.71	10	0.1083	-2211.83	2.76

Children 6 years ≤17

	Chi-square	D.F.*	p-value	log-likelihood	deviation** at 99th percentile
Normal	39.58	6	0.0000	-1653.92	2.58
Lognormal	3.22	8	0.9197	-1607.70	-1.50
Gamma	4.88	7	0.6745	-1609.33	-0.64
Weibull	24.48	6	0.0004	-1641.35	1.72
Wald	2.77	8	0.9480	-1609.64	-1.30

Men ≥18 years

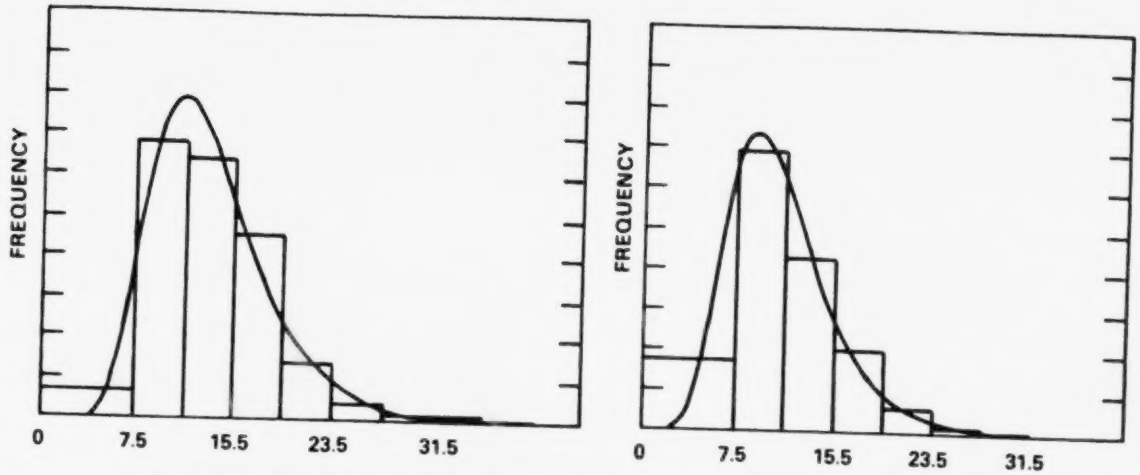
	Chi-square	D.F.*	p-value	log-likelihood	deviation** at 99th percentile
Normal	156.98	10	0.0000	-2952.85	6.24
Lognormal	12.22	13	0.5098	-2854.04	1.51
Gamma	34.26	12	0.0006	-2864.79	4.00
Weibull	132.91	11	0.0000	-2934.14	4.88
Wald	14.42	13	0.3450	-2855.94	1.72

Women ≥18 years

	Chi-square	D.F.*	p-value	log-likelihood	deviation** at 99th percentile
Normal	66.31	5	0.0000	-2631.67	2.68
Lognormal	7.70	8	0.4632	-2552.12	-1.18
Gamma	11.28	7	0.1267	-2553.34	0.90
Weibull	56.70	6	0.0000	-2611.78	1.73
Wald	10.26	8	0.2469	-2556.88	-1.01

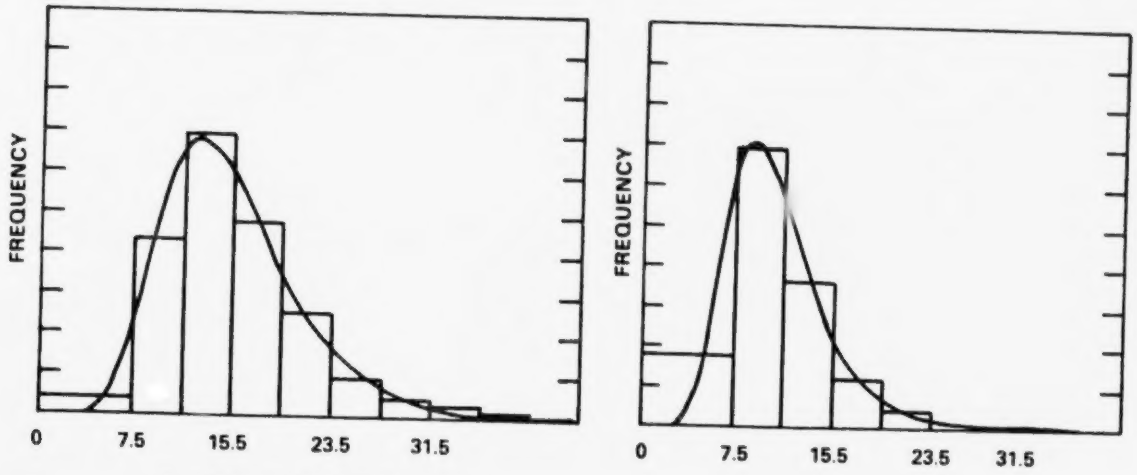
*D.F. = degrees of freedom.

**observed 99th sample percentile minus predicted 99th percentile.



BLOOD LEAD LEVELS, μg/dl, FOR 6-MONTH TO 6-YEAR-OLD-CHILDREN

BLOOD LEAD LEVELS, μg/dl, FOR 6-TO 17-YEAR OLD CHILDREN



BLOOD LEAD LEVELS, μg/dl, FOR MEN ⩾ 18 YEARS OLD

BLOOD LEAD LEVELS, μg/dl, FOR WOMEN ⩾ 18 YEARS OLD

Figure 11-6. Histograms of blood lead levels with fitted lognormal curves for the NHANES II study. All subgroups are white, non-SMSA residents, with family incomes over $6000/year.

Source: (EPA calculations from data supplied by National Center for Health Statistics.)

The Wald distribution is quite similar to the lognormal distribution and appears to provide almost as good a fit. Table 11-8 also indicates that the lognormal distribution estimates the 99th percentile as well as any other distribution.

Based on the examination of the NHANES II data, as well as the results of the several other studies discussed above, it appears that the lognormal distribution is the most appropriate for describing the distribution of blood lead levels in homogeneous populations with relatively constant exposure levels. The lognormal distribution appears to fit well across the entire range of the distribution, including the right tail.

The lognormal distribution describes both the mean and the variation of the populations under study. It is obvious that even relatively homogeneous populations have considerable variation among individuals. The estimation of this variation is important for determination of the proportion of individuals above a given blood lead level. This variation is the result of both analytic variation and population variation.

Analytic variation, which exists in any measurement of any kind, has an impact on the bias and precision of statistical estimates. For this reason, it is important to estimate the magnitude of variation. Analytic variation consists of both measurement variations (variation between measurements run at the same time) and variation created by analyzing samples at different times (days). This kind of variation for blood lead determinations has been discussed by Lucas (1981). The measurement variation alone does not follow a lognormal distribution, as was shown by Saltzman et al. (1983).

Values for the variation within groups (or mean square error) are available from several studies discussed above, including the NHANES II Survey, the N.Y. Childhood Screening Study, the Tepper-Leven Seven City Study, and the Azar et al. study. Variation, including analytic variation, ranged from about 1.3 to 1.4 when expressed as a geometric standard deviation. This value depends on the uniformness of the populations and the magnitude of the analytic variation.

The NHANES II study provides excellent data for the study of this variation, since it has excellent quality control and extensive information on demographic covariates. In order to minimize the effects of location, income, sex, and age, an analysis of variance procedure was used to estimate the variation for several age-race groups. The variables just mentioned were used as main effects, and the resulting mean square errors of the logarithms are shown in Table 11-9. The estimated geometric standard deviations have been adjusted for sex, age, income, and place of residence. As a result, the values for geometric standard deviations tend to be smaller than the unadjusted values for specific subgroups as reported by Annest and Mahaffey (1984).

TABLE 11-9. ESTIMATED MEAN SQUARE ERRORS RESULTING FROM ANALYSIS OF VARIANCE ON VARIOUS SUBPOPULATIONS OF THE NHANES II DATA USING UNWEIGHTED DATA

Age	White, Non-SMSA	White, SMSA, not central city	White, central city	Black, central city
0.5 to 6	0.0916 (1.35)*	0.0839 (1.34)	0.1074 (1.39)	0.0978 (1.37)
6 to 18	0.0814 (1.33)	0.0724 (1.31)	0.0790 (1.33)	0.0691 (1.30)
18+, men	0.1155 (1.40)	0.0979 (1.37)	0.1127 (1.40)	0.1125 (1.40)
18+, women	0.1083 (1.39)	0.0977 (1.37)	0.0915 (1.35)	0.0824 (1.33)

Note: Mean square errors are based on the logarithm of the blood lead levels.
*Estimated geometric standard deviations are given in parentheses.

The analytic variation was estimated specifically for this study by Annest et al. (1983b). The analytical variation was estimated as the sum of components estimated from the high and low blind pool and from the replicate measurements in the study of Griffin et al. (1975). The overall estimate of analytic variation for the NHANES II study was 0.02083 (estimated mean square error based on logarithms).

Analytic variation causes a certain amount of misclassification when estimates of the percent of individuals above or below a given threshold are made. This is because the true value of a person's blood lead could be below the threshold, but the contribution from analytic variation may push the observed value over the threshold. The reverse is also possible. These two types of misclassifications do not necessarily offset each other.

Annest et al. (1983b) estimated this misclassification rate for several subpopulations in the NHANES II data using a threshold value of 30 µg/dl. In general, the percent truly greater than this threshold was approximately 24 percent less than the prevalence of blood lead levels equal to or greater than 30 µg/dl, estimated from the weighted NHANES II data. This is less than the values predicted by Lucas (1981) which were based on some earlier studies.

The studies reviewed here provide estimates of geometric standard deviations for observed blood lead distributions which consistently fall in the range of 1.3 to 1.4. The NHANES II study, thought to provide the best available data set in terms of good quality control and other features such as sample size, yields estimates of geometric standard deviations for various subgroups of young children (0.5 to 6 years old) in the range of 1.34 to 1.39 (uncorrected for analytic error). Variations in the site means of log(blood lead) were calculated after controlling for race, income, and degree of urbanization. The remaining standard deviation of 0.183 for site means indicates substantial variation in baseline exposure after accounting for the major proxies for air lead. The geometric standard deviation attributable to the non-air lead exposure sources can be estimated by adjusting the NHANES II blood lead levels for the impact of gasoline lead by use of linear regression. Since gasoline lead during 1976-1980 accounted for 85 to 90 percent of air lead, the effect at gasoline lead = 0 was reduced by an additional 15 percent to account for all air lead. The resulting geometric standard deviation was 1.428. If this calculation is done only for children with blood lead < 40 μg/dl (who are more likely to be helped by an air lead standard) then the geometric standard deviation is 1.419. Thus, a geometric standard deviation for the NHANES II population of children without attribution of any source of lead exposure except gasoline lead and industrial air lead emissions may be taken as approximately 1.42.

11.3.5 Time Trends in Blood Lead Levels Since 1970

In the past few years a number of reports have appeared that examined trends in blood lead levels during the 1970's. In several of these reports some environmental exposure estimates are available.

11.3.5.1 Time Trends in NHANES II Study Data. Blood lead data from NHANES II (see section 11.3.3.1 for full discussion of methodology) show a significant downward trend over time for nationwide blood lead levels in the United States (Annest et al., 1983a). After accounting for the effects of race, sex, age, region of country, season, income, and degree of urbanization, a statistically significant negative association with date of sampling was found. Using regression model-predicted blood lead levels, a 37 percent drop from 14.6 to 9.2 μg/dl from the beginning to the end of the study was found. Overall nationwide mean blood lead levels from these data presented in 28-day intervals from February, 1976 to February, 1980 are displayed in Figure 11-7. Similar decreases in average blood lead levels were noted for a number of subgroups which compose the total sample (see Figure 11-8), with the declines ranging from 31 to 42 percent for various subgroups.

A variety of possible explanations for the nationwide decline in average blood lead levels were examined. Analysis of quality control samples indicated that laboratory drift was not the cause of the observed decline. Further statistical analyses ruled out the possibility that the decline was entirely due to season, income, geographic region, or urban-rural differences. Annest et al. (1983a) suggested that although strong correlation does not prove cause and effect, the most reasonable explanation for this trend appears to be reduction in the

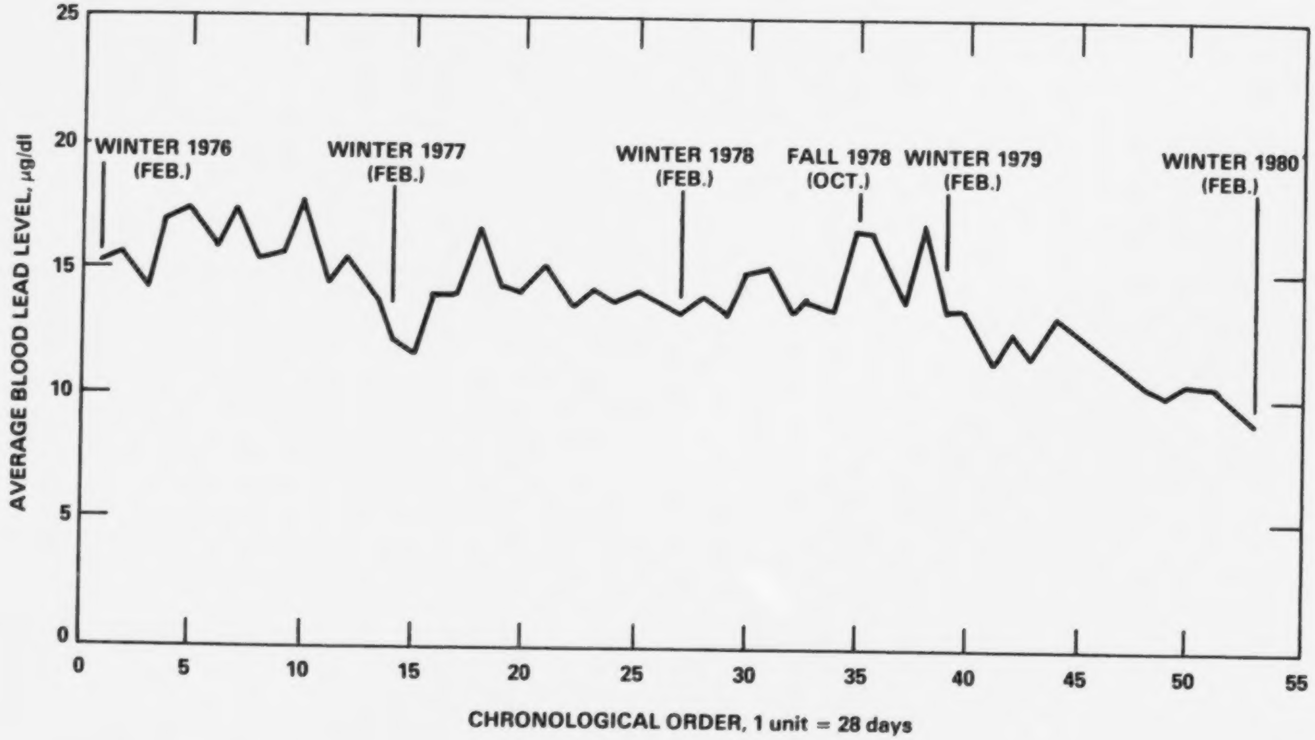


Figure 11-7. Average blood lead levels of U.S. population aged 6 months—74 years, United States, February 1976—February 1980, based on dates of examination of NHANES II examinees with blood lead determinations.

Source: Annest et al. (1983a).

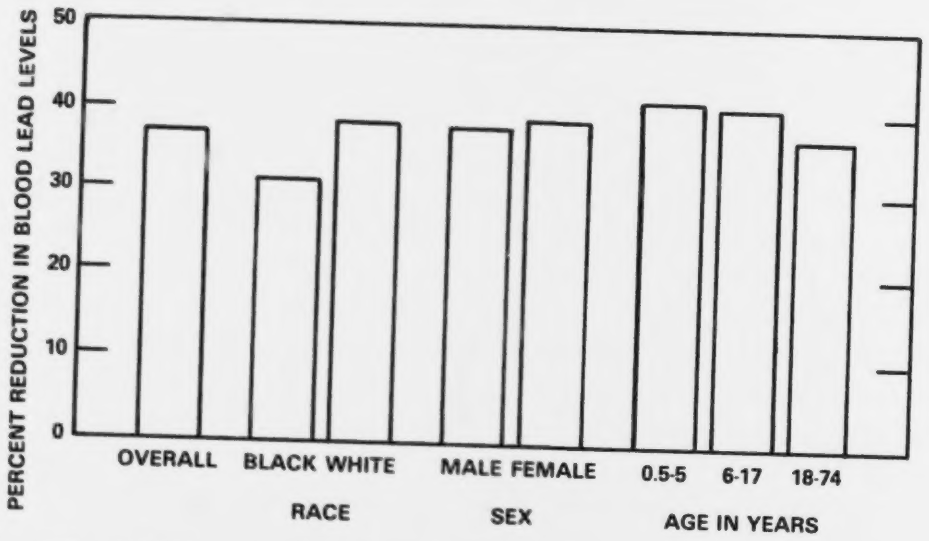


Figure 11-8. Reduction in mean blood lead levels, according to race, sex, and age. Data on sex and age are for whites.

Source: Annest et al. (1983a).

amount of lead used in gasoline production over the same time period (as discussed in more detail in Section 11.3.6.1).

11.3.5.2 Time Trends in the Childhood Lead Poisoning Screening Programs. Billick and colleagues have analyzed the results of blood lead screening programs conducted by the City of New York (Billick et al., 1979; Billick, 1982). Most details regarding this data set were already described, but Table 11-10 summarizes relevant methodologic information for these analyses and for analyses done on a similar data base from Chicago, Illinois. The discussion of the New York data below is limited to an exposition of the time trend in blood lead levels from 1970 to 1977.

Geometric mean blood lead levels decreased for all three racial groups and for almost all age groups in the period 1970-76 (Table 11-6). Table 11-11 shows that the downward trend covers the entire range of the frequency distribution of blood lead levels. The decline in blood lead levels showed seasonal variability, but the decrease in time was consistent for each season. The 1977 data were supplied to EPA by Dr. Billick.

In addition to this time trend observed in New York City, Billick (1982) examined similar data from Chicago and Louisville. The Chicago data set was much more complete than the Louisville one, and was much more methodologically consistent. Therefore, the Chicago data will mainly be discussed here. The lead poisoning screening program in Chicago may be the longest continuous program in the United States. Data used in this report covered the years 1967-1980. Because the data set was so large, only a 1 in 30 sample of laboratory records was coded for statistical analysis (similar to procedures used for New York described above).

The blood lead data for Chicago contains samples that may be repeats, confirmatory analyses, or even samples collected during treatment, as well as initial screening samples. This is a major difference from the New York City data, which had initial screening values only. Chicago blood lead levels were all obtained on venous samples and were analyzed by one laboratory, the Division of Laboratories, Chicago Department of Health. Lead determinations were done by atomic absorption. Racial composition was described in more detail than for New York, but analysis showed there was no difference among the non-blacks, so they were pooled in the final analysis.

Table 11-10 displays important characteristics of the Chicago and New York screening programs, including the number of observations involved in these studies. From tables in the appendices of the report (Billick, 1982), specific data on geometric mean blood lead values, race, sex, and sampling data for both cities are available. Consistency of the data across cities is depicted in Figure 11-9. The long-term trends are quite consistent, although the seasonal peaks are somewhat less apparent. Although the data displayed are only for blacks aged 25 to 36 months, very similar data are available for whites and other groups covered by the study.

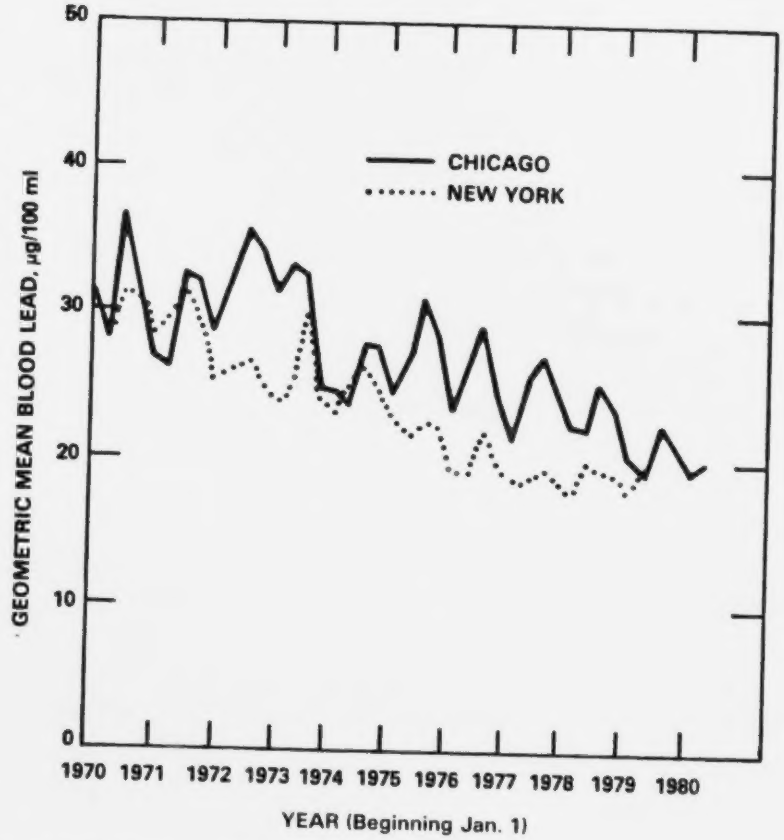


Figure 11-9. Time dependence of blood lead levels for blacks, aged 25-36 months, in New York City and Chicago.

Source: Adapted from Billick (1982).

TABLE 11-10. CHARACTERISTICS OF CHILDHOOD LEAD POISONING SCREENING DATA

	New York	Chicago
Time period	1970 - 1979	1967 - 1980 (QTR 2)
Sampling technique	Venous	Venous
Analytic technique	AAS (Hasel method)	AAS (Hasel method)
Laboratory	In house	In house
Screening status	Available/unknown	Unavailable
Race classification and total number of samples used in analysis*	Unknown 69,658 White 5,922 Black 51,210 Hispanic 41,364 Other 4,398 TOTAL 172,552	Nonblack 6,459 Black 20,353 TOTAL 26,812
Raw data	Decade grouped	Ungrouped
Gasoline data	Tri-state (NY, NJ, CT) 1970 - 1979 SMSA 1974 - 1979	SMSA

*New York data set only includes first screens while Chicago includes also confirmatory and repeat samples.

TABLE 11-11. DISTRIBUTION OF BLOOD LEAD LEVELS FOR 13- TO 48-MONTH-OLD BLACKS BY SEASON AND YEAR* FOR NEW YORK SCREENING DATA

	January - March Percent			July - September Percent		
Year	<15μg/dl	15 - 34μg/dl	>34μg/dl	<15μg/dl	15 - 34μg/dl	>34μg/dl
1970	(insufficient sample size)			3.4	54.7	42.0
1971	3.8	69.5	26.7	1.3	56.0	42.7
1972	4.4	76.1	19.5	4.3	72.2	23.4
1973	7.3	80.3	12.4	2.7	62.4	34.9
1974	9.2	73.8	17.0	8.2	65.4	26.4
1975	11.1**	77.5**	11.4**	7.3**	81.3**	11.4**
1976	21.1	74.1	4.8	11.9	75.8	12.3
1977	28.4	66.8	4.8	19.9	72.9	7.2

* data provided by I.H. Billick (1982).

**Percentages estimated using interpolation assuming a lognormal distribution.

11.3.5.3 Newark. Gause et al. (1977) present data from Newark, New Jersey, that reinforce the findings of Billick and coworkers. Gause et al. studied the levels of blood lead among 5- and 6-year-old children tested by the Newark Board of Education during the academic years 1973-74, 1974-75, and 1975-76. All Newark schools participated in all years. Participation rates were 34, 33, and 37 percent of the eligible children for the three years, respectively. Blood samples collected by fingerstick onto filter paper were analyzed for lead by atomic absorption spectrophotometry. The authors point out that fingerstick samples are more subject to contamination than venous samples; and that because erythrocyte protoporphyrin confirmation of blood lead values greater than 50 µg/dl was not done until 1974, data from earlier years may contain somewhat higher proportions of false positives than later years.

Blood lead levels declined markedly during the 3-year study period. The percentage of children with blood lead levels less than 30 µg/dl went from 42 percent for blacks in 1973-74 to 71 percent in 1975-76; similarly, the percentages went from 56 percent to 85 percent in whites. The percentage of high risk children (>49 µg/dl) dropped from 9 to 1 percent in blacks and from 6 to 1 percent in whites during the study period. Unfortunately, no companion analysis was presented regarding concurrent trends in environmental exposures.

Foster et al. (1979), however, reported a study from Newark that examined the effectiveness of the city's housing deleading program, using the current blood lead status of children who had earlier been identified as having confirmed elevated blood lead levels; according to the deleading program, these children's homes should have been treated to alleviate the lead problem. After intensive examination, the investigators found that 31 of the 100 children studied had lead-related symptoms at the time of Foster's study. Examination of the records of the program regarding the deleading activity indicated a serious lack of compliance with the program requirements. Given the results of Foster's study, it seems unlikely that the observed trend was primarily caused by the deleading program.

11.3.5.4 Boston. Rabinowitz and Needleman (1982) studied umbilical cord blood lead levels from 11,837 births between April, 1979 and April, 1981 in the Boston area. These represented 97 percent of the births occurring in a hospital serving a diverse population. Blood samples were analyzed for lead by anodic stripping voltammetry after stringent quality control procedures were used. External quality control checks were done by participation in the Blood Lead Reference Program, conducted by the Centers for Disease Control. The average difference between the investigators' results and the reference lab was 1.4 µg/dl.

The overall mean blood lead concentration was 6.56 ± 3.19 µg/dl (standard deviation) with a range from 0.0 to 37.0 µg/dl. After regression of the individual values of blood lead against the date of birth, a significant downward trend in blood levels was observed (∿0.89 µg/dl/yr), representing a decrease of 14 percent per year (Figure 11-10). Figure 11-10 also

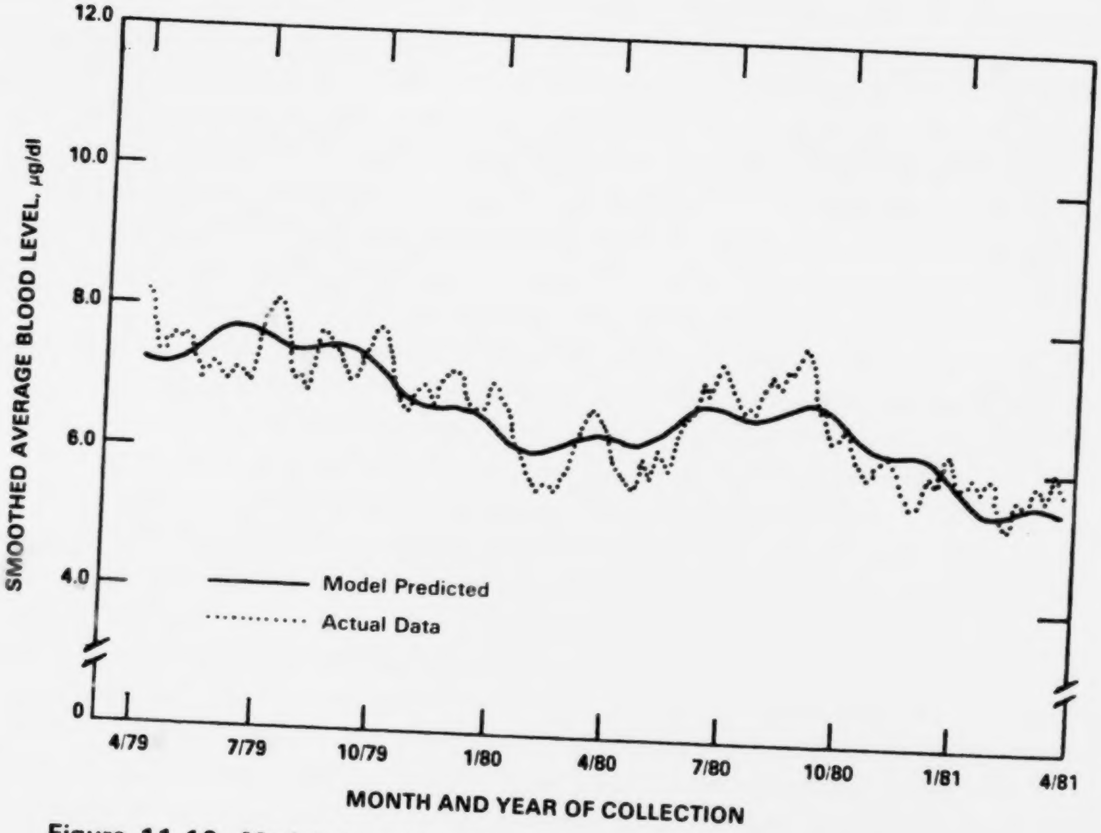


Figure 11-10. Modeled umbilical cord blood lead levels by date of sample collection for infants in Boston.

Source: Rabinowitz and Needleman (1982).

illustrates the complicating aspect of seasonal trends in evaluating underlying secular trends. The observed trend is similar to that noted in the NHANES II study described earlier. Rabinowitz and Needleman (1982) list the following as possible causes of the decline: (1) modification of the water supply to decrease the lead content; (2) reduction of the use of lead in gasoline; (3) reduction in contamination of food by solder; and 4) changes in prenatal practices, such as smoking or iron supplementation.

Rabinowitz and Needleman (1983) then sought to evaluate statistically possible reasons for the observed two-year downward trend in umbilical cord blood lead levels. The authors used pairwise product moment correlations for the monthly cord lead levels (about 500 per month) and monthly amounts of gasoline lead in Massachusetts. A strong correlation was observed: with the same month's data, the correlation coefficient was 0.716, which increased to a peak correlation coefficient of 0.758 when a 1-month lag time was used. The authors indicate that they did not observe similar trends in maternal tobacco smoking, education level, and alcohol consumption. They did observe a positive (instead of negative) trend in tap water lead concentrations. They conclude that gasoline lead exposure changes were probably the cause of the observed trend in blood lead levels.

From the ongoing surveillance of consecutive births, Rabinowitz et al. (1984) also identified a cohort of 249 infants who were enrolled in an ongoing cohort study after meeting certain eligibility standards. Indoor air was sampled for lead from the homes of children when each child was 6, 18, and 24 months of age. Tapwater was collected after a 4-liter flush, at 1 and 6 months of age. Seasonal biases in indoor/outdoor air lead ratios and the amounts of time spent indoors may have been confounding variables which may have distorted upward the underlying inhalation slope to the observed value near nine.

For each month there was generally available a mean air lead from 12 homes, water lead from 23 homes, and blood leads for 500 births. The study period covered March, 1980 to April, 1981. The blood leads were then correlated with gasoline lead sales, indoor air, and tapwater. A linear (although somewhat scattered) trend was found between lead in indoor air and gasoline lead sales. Forty-eight percent of the variance in air lead could be accounted for by the gasoline lead sales. Air lead and blood lead levels were highly correlated. The best linear fit ($r = 0.71$) has a slope of 9 $\mu g/dl/\mu g/m^3$ and an intercept of 4.9 $\mu g/dl$. No correlation was observed between water and blood lead levels. Interestingly, a higher correlation was found between gasoline lead sales and blood lead levels than between air lead and blood lead.

Karalekas et al. (1983) report additional data from the Boston metropolitan area. Results of the lead screening program indicate that the percentage of screened children with elevated blood lead levels declines over the period 1976-1981. Data on lead in water for this period are also presented. Water lead levels began to decline after the decline in blood lead levels. This relationship in this data warrants further research.

11.3.5.5 Lead Studies in the United Kingdom. There has been a series of publications from various workers in England who have been examining the question of whether or not time trends in blood lead levels exist there as well as in the United States (Oxley, 1982; Elwood, 1983a,b; Quinn, 1983). These papers cover a variety of exposure situations and populations studied. All of them obtained findings analogous to those described above for the United States, in that there has been a general decline in blood lead levels over the decade of the 1970's; they differ, however, with regard to the magnitude of the decline, when the decline began, and to what extent the decline may be attributable to a particular source of lead.

Oxley (1982) reported an analysis of blood lead levels found in blood samples drawn as a part of preemployment medical examinations conducted by a major U.K.-based oil company during 1967-69 and 1978-80. Blood samples were collected by venipuncture and analyzed for lead by two different methods. A comparative laboratory study also reported by Oxley suggested that the data could be adjusted from one method to the other. Geometric mean blood lead levels declined from 20.2 to 16.6 µg/dl.

Elwood (1983a) reported a time trend analysis of blood lead levels observed in adult women studied over a 10-year period in eight surveys conducted in a variety of locations in Wales. These were analyzed and examined for trends in blood lead levels. All women included in this analysis came from surveys which were designed to generate representative samples of adult women in residential areas. A high response rate (90 percent or more) was obtained in each of the surveys. Venous blood samples were collected and analyzed for lead. A single laboratory performed all of the analyses with an external reference laboratory performing quality control checks in some of the surveys. Overall mean blood lead levels for the various surveys fell more than 30 percent over the period 1972-1982. Two of the surveys were conducted in the same area. Between 1974 and 1982, the mean blood lead concentration fell 37 percent. Surveys from mining areas showed that women there had higher blood lead levels than in non-mining areas.

Elwood acknowledges that laboratory drift may be present in the data and also that the surveys did not generate strictly comparable samples. Still, the observed decline was thought to be real. No statistical analysis of the data is presented to examine the possible reasons for the observed decline, but a number of possible environmental reasons were discussed. Reduced gasoline lead exposures as a reason were dismissed on the basis that while the lead concentration in gasoline had indeed declined, the overall use of petrol in England had increased, therefore balancing the reduction. However, no data regarding traffic patterns or gasoline usage in Wales were presented to verify this reasoning. A portion (amount unspecified) of the reduction was attributed to a drop in dietary intake of lead due to the reduced use of canned foods.

Elwood (1983b) also presents data from a more homogeneous setting. In 1969 a hematologic survey of a random sample of 4070 women was conducted in one town in Wales. Detailed studies were made of 121 of these women whose hemoglobin levels were below 10.5 g/100 ml. Samples of their whole blood were deep frozen, and follow-up samples were obtained for some of the same women in 1982. Follow-up and loss of original samples resulted in there being 26 women with an available blood lead at both times and who were still living at the same address. The mean fall in blood lead levels for these women was 23 percent, representing a fall of 3.5 µg/100 ml. Again Elwood does not attribute the decline to changes in gasoline lead or water supply, but instead suggests that it may be due to changes in dietary intake although noting there are no data on which to base a judgment.

King (1983), in commenting on the results of Elwood (1983a), noted that the blood lead values before 1975 were probably falsely elevated due to matrix problems in the chemical analysis. This means the magnitude of the observed decline is probably less than that quoted by Elwood (1983b). King (1983) further examined the question of the time trend by controlling for region of Wales and reported that Elwood's data showed a 50 percent increase in blood lead levels from 1981 to 1982, a most unlikely outcome. Pirkle and Annest (1984) have also criticized the Elwood (1983a) paper and concluded that various factors make reliable interpretations of Elwood's data extremely difficult.

Quinn (1983) reports on the summarized findings of two large-scale survey effects in 1979 and 1981. Broad comparisons within the same authority showed an overall reduction approaching 10 percent (1 µg/100 ml). Quinn himself states, however, that these two survey efforts are not strictly comparable in that the first round focused on representative population groups while the second round focused on areas where lead may have presented a problem. No effort was made to attribute the decline in blood lead levels to a particular source.

11.3.5.6 Other Studies. Okubo et al. (1983) examined a total of 1933 children from 5 to 18 years of age for blood lead using the Hessel method over the period 1975 to 1980 in an urban area of Tokyo and in a nearby suburban area. The analysis of all blood lead was done by the same laboratory. Over the time period of the study an apparent decrease in blood lead is shown. A part of the difference in blood lead between urban and suburban groups is related to the difference in average lead concentrations between the two areas. The difference of blood lead between urban and suburban becomes greater when the comparison of blood lead between the two areas is executed only among children who have lived in the same areas from their birth.

In an international study discussed in detail earlier, Friberg and Vahter (1983) compared data on blood lead levels obtained in 1967 with data for 1981 (see Table 11-12). For areas of

TABLE 11-12. COMPARISON OF MEDIAN BLOOD LEAD LEVELS (μg/dl) IN SEVERAL COUNTRIES FROM STUDIES OF GOLDWATER AND HOOVER (1967) AND FRIBERG AND VAHTER (1983)

Country	Median blood lead 1967	Median blood lead 1981	% change from 1967
Japan	21.0	6.0	71
Israel	15.0	8.2	45
United States	18.0	7.5	58
Yugoslavia	15.0	9.2	39

the world where there were data collected by Goldwater and Hoover (1967) as well as the UN/WHO study, there has been a substantial reduction in reported blood lead levels. A cautionary note must be made, however, that the analytic and human sampling procedures are not the same in the two studies. Therefore these data should be thought of as providing further but limited evidence supporting a recent downward trend in blood lead levels worldwide.

11.3.6 Gasoline Lead as an Important Determinant of Trends in Blood Lead Levels

As noted in the preceding section, explanations have been sought for declining trends in blood lead levels observed among population groups in the United States and certain other countries since the early 1970s. Also noted was evidence presented by some investigators which strongly suggests that gasoline lead usage is a major determinant of the reported downward trends in blood lead levels. The present section examines additional, extensive evidence which points towards gasoline lead being an important determinant of changes in blood lead levels associated with exposures to airborne lead of populations in the United States and elsewhere.

11.3.6.1 NHANES II Study Data. Blood lead data from the second National Health and Nutrition Examination survey (NHANES II) were described earlier in Sections 11.3.3.1 and 11.3.5.1. One striking feature of the NHANES II data was a dramatic decline in nationwide average blood lead levels in the United States during the period (1976 to 1980) of the survey. In evaluating possible reasons for the observed decrease in the NHANES II blood lead values, Annest et al. (1983a) found highly significant associations between the declining blood lead concentrations for the overall U.S. population and decreasing amounts of lead used in gasoline in the U.S. during the same time period (see Figure 11-11). The associations persisted after adjusting for race, age, sex, region of the country, season, income, and degree of urbanization (see Table 11-13). Analogous strong associations ($r = 0.95$; $p < 0.001$) were also found for blood lead levels for white children aged 6 months to 5 years in the NHANES II sample and gasoline lead usage (Annest et al., 1983a).

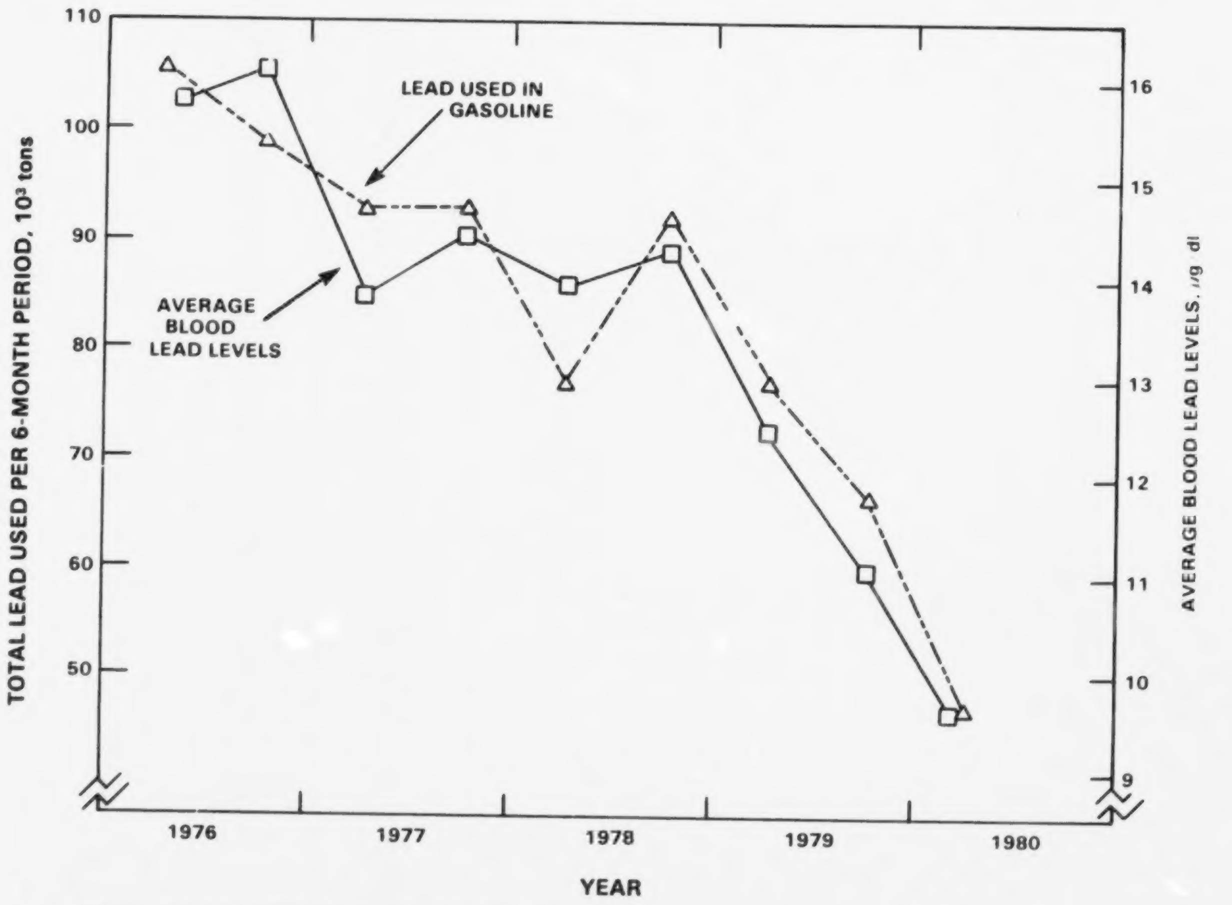


Figure 11-11. Parallel decreases in blood lead values observed in the NHANES II study and amounts of lead used in gasoline during 1976-1980.

Source: Annest (1983).

11-13. PEARSON CORRELATION COEFFICIENTS BETWEEN THE AVERAGE BLOOD LEAD LEVELS FOR SIX-MONTH PERIODS AND THE TOTAL LEAD USED IN GASOLINE PRODUCTION PER SIX MONTHS, ACCORDING TO RACE, SEX, AND AGE[a]

	Coefficients for 6-month periods[b]		
	January-June and July-December[c]	April-September and October-March[d]	Averages
Overall (all races)	0.920	0.938	0.929
All black[e]	0.678	0.717	0.698
All whites	0.929	0.955	0.942
By sex: Male	0.944	0.960	0.952
Female	0.912	0.943	0.928
By age: 0.5-5 yr	0.955	0.969	0.962
6-17 yr	0.908	0.970	0.939
18-74 yr	0.920	0.924	0.922

[a] The lead values used to compute the averages were preadjusted by regression analysis to account for the effects of income, degree of urbanization, region of the country, season, and, when appropriate, race, sex, and age.

[b] All correlation coefficients were statistically significant ($p < 0.001$) except those for blacks ($p < 0.05$).

[c] Averages were based on six-month periods, except for the first and last time periods , which covered only February 1976 through June 1976 and January 1980 through February 1980, respectively.

[d] Averages were based on six-month periods, except for the last time period, which covered only October 1979 through February 1980.

[e] Blacks could not be analyzed according to sex and age subgroups because of inadequate sample sizes.

Questions have been raised by some commentors regarding whether or not (1) the NHANES II survey design was adequate to allow for credible definition of time trends for nationwide average blood lead concentrations, (2) the reported significant associations between NHANES II blood lead data and U.S. gasoline usage are credible and reflect a causal relationship, and (3) the entire decline in blood lead values is attributable to decreased gasoline lead usage versus changes in other sources of lead exposure. These issues and alternative analyses concerning the NHANES II blood lead/gasoline lead relationships were evaluated by an expert panel (the NHANES II Time-Trend Analysis Review Group) convened by EPA.

The NHANES II Time-Trend Analysis Review Group (1983) found the following: (1) strong evidence that there was a substantial decline in the average level of blood lead in the U.S. population during the NHANES II survey period; (2) after adjustment for relevant demographic covariables, the magnitude of the change can be estimated for the total U.S. population and for some major subgroups, provided careful attention is given to underlying model assumptions. The Review Group also found a strong correlation between gasoline-lead usage and blood-lead levels, and noted that in the absence of scientifically plausible alternative explanations, the hypothesis that gasoline lead is an important causal factor for blood-lead levels must receive serious consideration. Nevertheless, despite the strong association between the decline in gasoline-lead usage and the decline in blood-lead levels, the survey results and statistical analyses do not confirm the causal hypothesis. Rather, this finding is based on the qualitatively consistent results of extensive analyses done in different but complementary ways.

Further support for strong, likely causative, relationships between gasoline lead usage and blood lead levels in the U.S. is provided by analyses carried out by Schwartz et al. (1984). Those analyses not only evaluated NHANES II data, but, also, additional blood lead data such as blood lead values from U.S. childhood lead-screening programs. Results obtained were quite similar to those of Annest et al. (1983b), even after controlling for possible alternative contributors to the blood lead decline, e.g., deleading of lead-painted housing units or decreased food lead intake. Large numbers (thousands) of children were also estimated by the analysis to have blood lead levels in excess of 30 µg/dl due in part to exposures to lead emitted as a consequence of leaded gasoline usage in the United States.

Still further evidence for causative relationships between gasoline lead usage and changes in human blood lead levels is provided by isotope studies of the type described next.

11.3.6.2 Isotope Studies. Two field investigations have attempted to derive estimates of the amount of lead from gasoline that is absorbed by the blood of individuals. Both of these investigations used the fact that non-radioactive isotopes of lead are stable. The varying proportions of the isotopes present in blood and environmental samples can indicate the source of the lead. The Isotopic Lead Experiment (ILE) is an extensive study that attempted to use differing proportions of the isotopes in geologic formations to infer the proportion of lead in gasoline that is absorbed by the body. The other study used existing natural shifts in isotopic proportions in an attempt to do the same thing.

11.3.6.2.1 Italy. The ILE is a large-scale community study in which the geologic source of lead for antiknock compounds in gasoline was manipulated to change the isotopic composition of the atmosphere (Garibaldi et al., 1975; Facchetti, 1979; Facchetti, 1985). Preliminary investigation of the environment of Northwest Italy, and the blood of residents there, indicated that the ratio of $^{206}Pb/^{207}Pb$ in blood was a constant, about 1.16, and the ratio in gasoline was about 1.18. This preliminary study also suggested that it would be possible to substitute for the currently used geologic sources of lead for antiknock production a geologically distinct source of lead from Australia that had an isotopic $^{206}Pb/^{207}Pb$ ratio of 1.04. It was hypothesized that the resulting change in blood lead $^{206}Pb/^{207}Pb$ ratios (from 1.16 to a lower value) would indicate the proportion of lead in the blood of exposed human populations attributable to lead in the air contributed by gasoline combustion in the study area.

Baseline sampling of both the environment and residents in the geographic areas of the study was conducted in 1974-1975. The sampling included air, soil, plants, lead stock, gasoline supplies, etc. Human blood sampling was done on a variety of populations within the area. Both environmental and human samples were analyzed for lead concentrations as well as isotopic $^{206}Pb/^{207}Pb$ composition.

In August, 1975, the first switched (Australian lead-labeled) gasoline was introduced; although it was originally intended to get a 100 percent substitution, practical and logistical problems resulted in only a 50 percent substitution being achieved by this time. By May, 1977, these problems were worked out and the substitution was practically complete. The substitution was maintained until the end of 1979, when a partial return to use of the original sources of lead began. Therefore, the project had four phases: phase zero - background; phase one - partial switch; phase two - total switch; and phase three - switchback.

Airborne lead measurements were collected in a number of sites to generate estimates of the lead exposure that was experienced by residents of the area. Turin, the major city of the region, was found to have a much greater level of atmospheric lead than the surrounding countryside. There also appeared to be fairly wide seasonal fluctuations.

The isotopic lead ratios obtained in the samples analyzed are displayed in Figure 11-12. It can easily be seen that the airborne particulate lead rapidly changed its isotope ratio in line with expectations. Changes in the isotope ratios of the blood samples appeared to lag somewhat behind. Background blood lead ratios for adults were 1.1591 ± 0.0043 in rural areas and 1.1627 ± 0.0022 in Turin in 1975. For Turin adults, a mean isotopic ratio of 1.1325 was obtained in 1979, clearly less than background. Isotopic ratios for Turin schoolchildren, obtained starting in 1977, tended to be somewhat lower than the ratios for Turin adults.

Preliminary analysis of the isotope ratios in air lead allowed for the estimation of the fractional contribution of gasoline in the city of Turin, in small communities within 25 km of Turin, and in small communities beyond 25 km (Facchetti and Geiss, 1982). At the time of maximal use of Australian lead isotope in gasoline (1978-1979), about 87.3 percent of the air

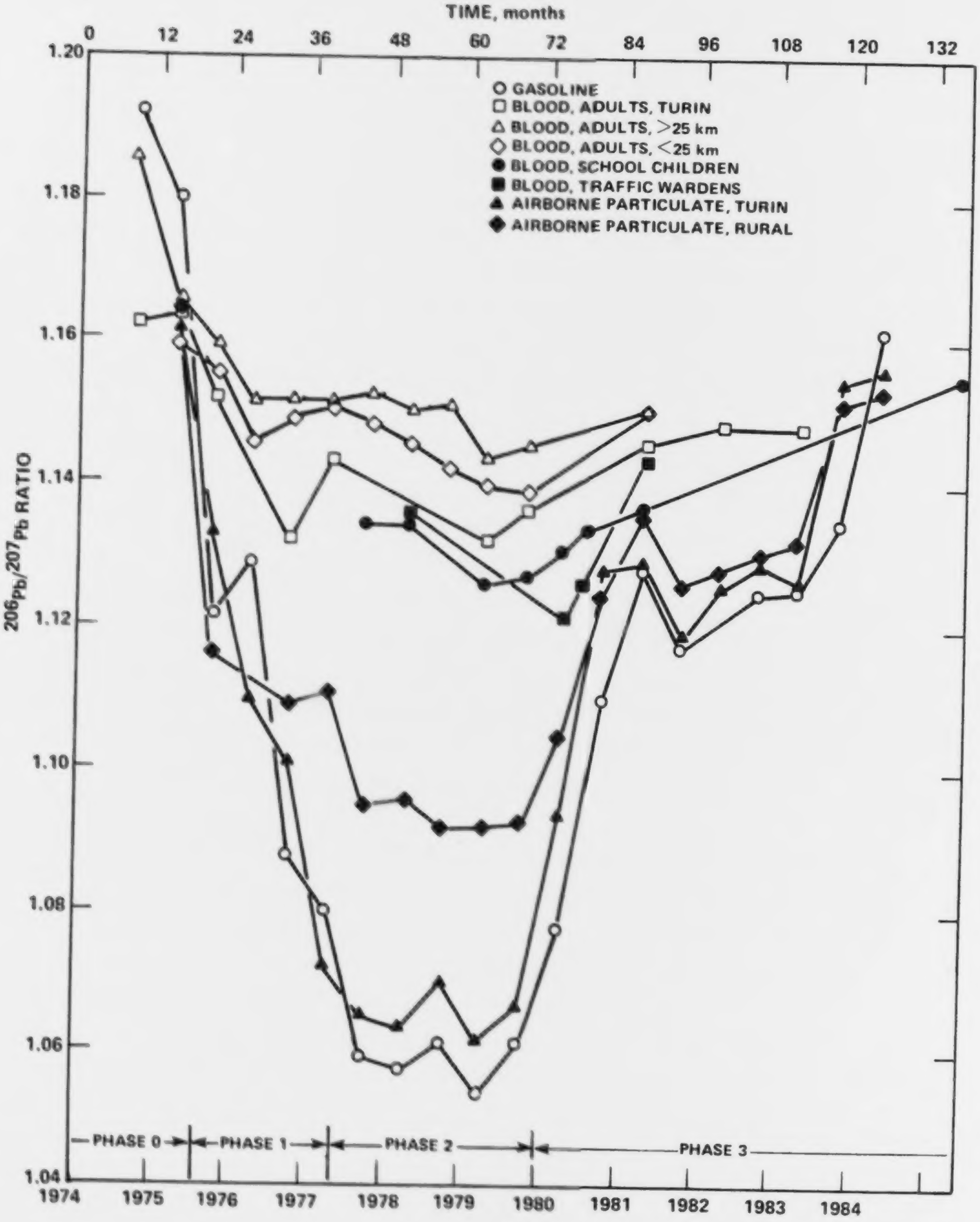


Figure 11-12. Change in ^{206}Pb/^{207}Pb ratios in gasoline, blood, and airborne particulate from 1974 to 1984.

Source: Facchetti (1985).

lead in Turin and 58.7 percent of the air lead in the countryside was attributable to gasoline. The determination of lead isotope ratios was essentially independent of air lead concentrations. During that time, air lead averaged about 2.0 μg/m^3 in Turin (from 0.88-4.54 μg/m^3 depending on location of the sampling site), about 0.56 μg/m^3 in the nearby communities (0.30-0.67 μg/m^3) and about 0.30 μg/m^3 in more distant (> 25 km) locations. It is important to note that the contribution calculations are for local lead in gasoline, not all lead from gasoline. Large movements of air masses brought in air lead from other regions, especially for the suburban and urban areas. In the absence of nearby lead industrial sources, this air lead was at least substantially composed of non-Australian gasoline lead and would therefore lead to an underestimate of the total contribution of gasoline lead to blood lead.

Blood lead concentrations and isotope ratios for 63 adult subjects were determined on two or more occasions during phases 0-2 of the study. Their blood lead isotope ratios decreased over time and the fraction of lead in their blood attributable to the Australian lead-labeled gasoline could be estimated independently of blood lead concentration (see Appendix C for estimation method). The mean fraction of blood lead attributable to the Australian lead-labeled gasoline ranged from 21.4 ± 10.4 percent in Turin to 11.4 ± 7.3 percent in the nearby (< 25 km) countryside and 10.1 ± 9.3 percent in the remote countryside. These likely represent minimal estimates of fractions of blood lead derived from gasoline due to the following reasons: (1) use of some non-Australian lead-labeled gasoline brought into the study area from outside; (2) probable insufficient time to have achieved steady-state blood lead isotope ratios by the time of the switchback; and (3) probable insufficient time to fully reflect delayed movement of the Australian lead from gasoline via environmental pathways in addition to air.

These results can be combined with the actual blood lead concentrations to estimate the fraction of gasoline uptake attributable or not attributable to direct inhalation. The results are shown in Table 11-14 based upon the concept outlined in Facchetti and Geiss (1982). From Section 11.4.1, we conclude that an assumed value of $\beta=1.6$ is plausible for predicting the amount of lead absorbed into blood at air lead concentrations less than 2.0 μg/m^3. The predicted values for lead from gasoline in air (in the ILE) range from 0.28 to 2.79 μg/dl in blood due to direct inhalation. The total contribution to blood lead from gasoline is much larger, from 3.21 to 4.66 μg/dl, suggesting that the non-inhalation contribution of gasoline increases from 1.88 μg/dl in Turin to 2.33 μg/dl in the near region and 2.93 μg/dl in the more distant region. The non-inhalation sources include ingestion of dust and soil lead, and lead in food and drinking water. Efforts are being made to quantify the magnitude of these sources. The average direct inhalation of lead in the air from gasoline

TABLE 11-14. ESTIMATED CONTRIBUTION OF LEADED GASOLINE TO BLOOD LEAD BY INHALATION AND NON-INHALATION PATHWAYS

Location	Air Pb fraction from gasoline(a)	Mean air Pb conc.,(b) μg/m³	Blood Pb fraction from gasoline(c)	Mean blood Pb conc.,(d) μg/dl	Blood Pb from gasoline,(e) μg/dl	Pb from gasoline in air,(f) μg/dl	Non-inhaled Pb from gaso line,(g) μg/dl	Estimated fraction gas-Pb inhalation(h)
Turin	0.873	2.0	0.214	21.77	4.66	2.79	1.88	0.60
<25 km	0.587	0.56	0.114	25.06	2.86	0.53	2.33	0.19
>25 km	0.587	0.30	0.101	31.78	3.21	0.28	2.93	0.09

(a) Fraction of air lead in Phase 2 attributable to lead in gasoline.

(b) Mean air lead in Phase 2, μg/m³.

(c) Mean fraction of blood lead in Phase 2 attributable to lead in gasoline.

(d) Mean blood lead concentration in Phase 2, μg/dl.

(e) Estimated blood lead from gasoline = (c) x (d)

(f) Estimated blood lead from gasoline inhalation = β x (a) x (b), β = 1.6.

(g) Estimated blood lead from gasoline, non-inhalation = (f)-(e)

(h) Fraction of blood lead uptake from gasoline attributable to direct inhalation = (f)/(e)

Data: Facchetti and Geiss (1982); Facchetti (1985).

is 9 to 19 percent of the total intake attributable to gasoline in the countryside and an estimated 60 percent in the city of Turin. Note that in this sample, the blood lead concentrations were lowest in the city and highest in the more remote areas. This is not obviously attributable to sex because the city sample was all male. Facchetti (1985) notes that factors unaccounted for are presumably acting on the population of the ILE test area. The lead concentration in tapwater in Turin is approximately 4 μg/l, while it ranges in the country from 12 to 20 μg/l. Also, lead concentrations in Piedmont wines averaged 155 ± 67 μg/l. Daily wine consumption for rural drinkers ranges from 0.5 to 1 liter per day. Thus the importance of wine consumption becomes evident. Other differences between city and county may play a role. A more detailed statistical investigation is needed.

Spengler et al. (1984) have developed a modeling approach to try to explain these results. Their hypothesized model suggests that in-vehicle lead exposure is important and may explain part of the apparent anomaly of the blood lead levels in this study. That is, Spengler et al. (1984) hypothesized that there is a large component of personal lead exposure associated with gasoline use that is not captured by stationary ambient air lead monitors:

personal exposure while riding in and working around motor vehicles using leaded gas. More work on this problem is needed, particularly conduction of near- and in-vehicle studies.

Lead uptake may also be associated with occupation, sex, age, smoking, and drinking habits. The linear exposure model used in Section 11.4 was also used here to estimate the fraction of labeled blood lead from gasoline attributable to exposure via direct inhalation and other pathways. EPA used the data in Facchetti and Geiss (1982) for the 35 subjects for whom repeated measurements allowed estimation of the change in isotope ratios in the blood. Their blood lead concentrations in Phase 2 were also determined, allowing for estimation of the total gasoline contribution to blood lead. Possible covariates included sex, age, cigarette smoking, drinking alcoholic beverages, occupation, residence location, and work location. In order to obtain some crude comparisons with the inhalation exposure studies of Section 11.4.1, EPA analyses assigned the air lead values listed in Table 11-15 to various locations. Lower values for air lead in Turin would increase the estimated blood lead inhalation slope above the estimated value of 1.70. Since the fraction of time subjects were exposed to workplace air was not known, this was also estimated from the data as about 41 percent (i.e., 9.8 hours/ day). The results are shown in Figure 11-13 and Table 11-16. Of all the available variables, only location, sex, and inhaled air lead from gasoline proved statistically significant in predicting blood lead attributable to gasoline. The model predictability is fairly good, with an R^2 value of 0.654. It should be noted that a certain amount of confounding of variables was unavoidable in this small set of preliminary data, e.g., no female subjects in Turin or in occupations of traffic wardens, etc. There was a systematic increase in estimated non-inhalation contributions from gasoline use for remote areas, but the cause is unknown. The following interpretation for these results may be offered: The air lead measurements used here represent community or ambient exposures. In addition to the ambient air lead, there may have also been systematic differences in personal exposure. Nevertheless, the estimated non-inhalation contribution of gasoline to blood lead in the ILE study is significant (i.e., 1.8-3.4 μg/dl).

TABLE 11-15. ASSUMED AIR LEAD CONCENTRATIONS FOR MODEL

Residence or workplace code	1-4	5	6
Location	outside Turin	Turin residential	Turin central
Air lead concentration	(a)	1.0 μg/m^3(b)	2.5 μg/m^3(c)

(a) Use value for community air lead, 0.16 - 0.67 μg/m^3.

(b) Intermediate between average traffic areas (1.71 μg/m^3) and low traffic areas (0.88 μg/m^3) in Turin.

(c) Intermediate between average traffic areas (1.71 μg/m^3) and heavy traffic areas (4.54 μg/m^3) in Turin.

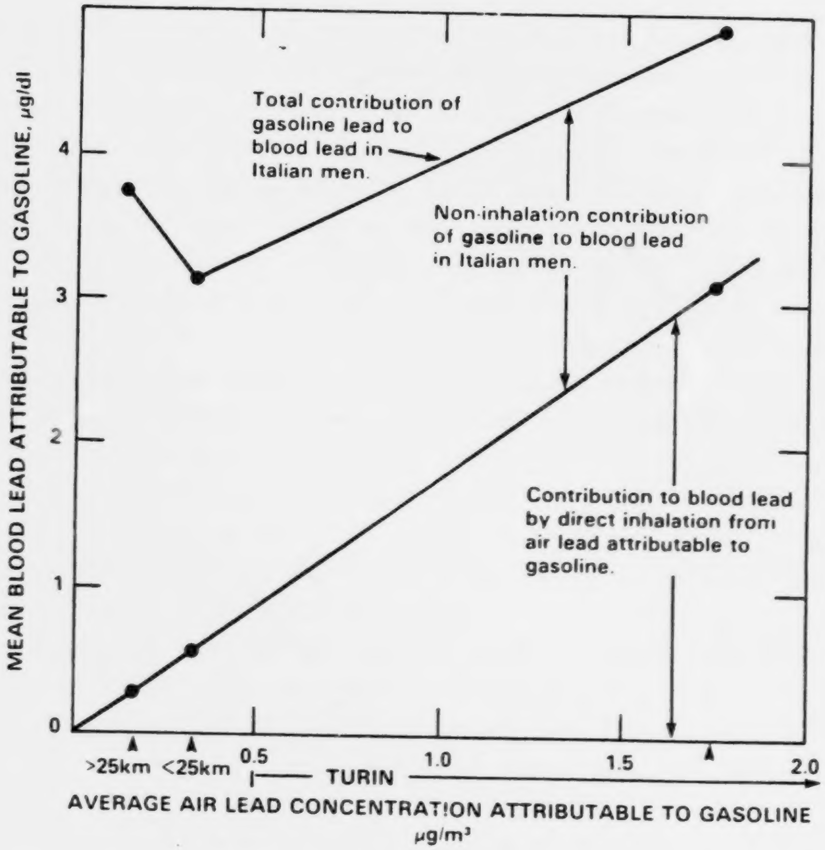


Figure 11-13. Estimated direct and indirect contributions of lead in gasoline to blood lead in Italian men, based on EPA analysis of ILE data (Table 11-16).

TABLE 11-16. REGRESSION MODEL FOR BLOOD LEAD ATTRIBUTABLE TO GASOLINE

Variable	Coefficient ± standard error
Air lead from gas	1.70 ± 1.04 µg/dl per µg/m³
Location	
Turin	1.82 ± 2.01 µg/dl
<25 km	2.56 ± 0.59 µg/dl
>25 km	3.42 ± 0.85 µg/dl
Sex	-2.03 ± 0.48 µg/dl for women

The preliminary linear analysis of the overall ILE data set (2161 observations) found that total blood lead levels depended on other covariates for which there were plausible mechanisms of lead exposure, including location, smoking, alcoholic beverages, age, and occupation (Facchetti and Geiss, 1982). The difference between total blood lead uptake and blood lead uptake attributable to gasoline lead has yet to be analyzed in detail, but these analyses suggest that certain important differences may be found. Some reservations have been expressed about the ILE study, both by the authors themselves and by Elwood (1983c). These include unusual conditions of meteorology and traffic in Turin, and demographic characteristics of the 35 subjects measured repeatedly that may restrict the generalizability of the study. Facchetti (1985) reports additional analysis which increases the number of blood leads from 35 to 63, alleviating this concern to some extent since the new results confirm the old. However, it is clear that changes in air lead attributable to gasoline were tracked by changes in blood lead in Turin residents. The airborne particulate lead isotope ratio quickly achieved new equilibrium levels as the gasoline isotope ratio was changed, and maintained that level during the 2½ years of Phase 2. The blood lead isotope ratios fell slowly during the changeover period, and rose again afterwards as shown in Figure 11-12. Equilibrium was not clearly achieved for blood lead isotope ratios, possibly due to large endogenous pools of old lead stored in the skeleton and slowly mobilized over time. Even with such reservations, this study provides a useful basis for relating blood lead and air lead derived from gasoline combustion. Colombo and Fantechi (1983) have presented an analysis of the ILE study using a dynamic model. The results of their analysis suggest that an appropriate estimate of the contribution of locally consumed gasoline lead to blood lead is 26, 17, and 14 percent for the subject groups of Turin, and near and far countryside, respectively. These values are similar to but somewhat larger than those presented by Facchetti and Geiss (1982) and Facchetti (1985).

11.3.6.2.2 United States. Manton (1977) conducted a long-term study of 10 subjects whose blood lead isotopic composition was monitored for comparison with the isotopic composition of the air they breathed. Manton had observed that the ratio of $^{206}Pb/^{204}Pb$ in the air varied with seasons in Dallas, Texas; therefore, the ratio of those isotopes should vary in the blood. By comparing the observed variability, estimates could then be made of the amount of lead in air that is absorbed by the blood.

Manton took monthly blood samples from all 10 subjects from April, 1974 until June, 1975. The blood samples were analyzed for both total lead and isotopic composition. The recruited volunteers included a mix of males and females, and persons highly and moderately exposed to lead. However, none of the subjects was thought to be exposed to more than 1 $\mu g/m^3$ of lead in air. Lead in air samples was collected by hi-vol samplers primarily from one site in Dallas. That site, however, had been shown earlier to vary in isotopic composition paralleling another site some 16 miles away. All analyses were carried out under clean conditions with care and caution being exercised to avoid lead contamination.

The isotope ratio of $^{206}Pb/^{204}Pb$ increased linearly with time from about 18.45 to 19.35, approximately a 6 percent increase. At least one of the two isotopic lead ratios increased linearly in 4 of the 10 subjects. In one other, they increased, but erratically. In the remainder of the subjects, the isotopic ratios followed smooth curves showing inflection points. The curves obtained for the two subjects born in South Africa were 6 months out of phase with the curves of the native-born Americans. The fact that the isotope ratios in 9 of the 10 subjects varied regularly was thought to indicate that the non-airborne sources of lead varied in isotopic composition very slowly.

The blood lead levels exhibited a variety of patterns, although none of the subjects showed more than a 25 percent change from initial levels. This suggests a reasonably steady-state external environment.

Manton carried his analyses further to estimate the percentage of lead in blood that comes from air. He estimated that the percentage varied from 7 to 41 percent, assuming that dietary sources of lead had a constant isotopic ratio while air varied. He calculated the percent contribution according to the following equation.

$$\frac{q}{100+q} = \frac{b}{a}, \quad \text{where} \qquad (11\text{-}1)$$

b = rate of change of an isotope ratio in blood,

a = rate of change of the same ratio in the air, and

q = constant defined as the number of atoms of the isotope in the denominator of the airborne lead ratio mixed with 100 atoms of the same isotope of lead from non-airborne sources.

The results are shown in Table 11-17. Slopes were obtained by least squares regression. Percentages of airborne lead in blood varied between 7 ± 3 and 41 ± 3.

Stephens (1981) extended the analysis of data in Manton's study (Table 11-18). He used the observed air lead concentrations based on actual 24-hour air lead exposures in three adults. He assumed values for breathing rate, lung deposition, and absorption into blood to estimate the blood lead uptake attributable to ^{204}Pb by the direct inhalation pathway. Subjects 5, 6, and 9 absorbed far more air lead in fact than was calculated using the values in Table 11-17. The total air lead contribution for those subjects was 8.4, 4.4, and 7.9 times, respectively, larger than the direct inhalation. These estimates are sensitive to the assumed parameter values.

TABLE 11-17. RATE OF CHANGE OF $^{206}Pb/^{204}Pb$ AND $^{206}Pb/^{207}Pb$ IN AIR AND BLOOD, AND PERCENTAGE OF AIRBORNE LEAD IN BLOOD OF SUBJECTS 1, 3, 5, 6, AND 9

Subject	Rate of change per day		Percentage of airborne lead in blood	
	$^{206}Pb/^{204}Pb$ X 10^{-4}	$^{206}Pb/^{207}Pb$ X 10^{-5}	From $^{206}Pb/^{207}Pb$	From $^{206}Pb/^{207}Pb$
(Air)	17.60 ± 0.77	9.97 ± 0.42	. . .	. . .
1	. . .	0.70 ± 0.30	. . .	7 ± 3
3	5.52 ± 0.55	. . .	31.4 ± 3.4	. . .
5	. . .	3.13 ± 0.34	. . .	31.4 ± 3.7
6	6.53 ± 0.49	4.10 ± 0.25	37.1 ± 2.8	41.1 ± 3.0
9*	3.25	2.01	18.5	20.0

Note: Errors quoted are one standard deviation

*From slope of tangent drawn to the minima of subject's blood curves. Errors cannot realistically be assigned.

TABLE 11-18. CALCULATED BLOOD LEAD UPTAKE FROM AIR LEAD USING MANTON ISOTOPE STUDY

					Blood uptake from air		
Subject	Concentration	Exposure*	Deposition*	Absorption*	Calculated inhalation	Observed	Fraction of lead uptake from gasoline by direct inhalation
5	0.22 μg/m^3	15 m^3/day	37%	50%	0.61 μg/d	5.1 μg/d	0.120
6	1.09 μg/m^3	15 m^3/day	37%	50%	3.0 μg/d	13.2 μg/d	0.229
9	0.45 μg/m^3	15 m^3/day	37%	50%	1.2 μg/d	9.9 μg/d	0.126

*assumed rather than measured exposure, deposition and absorption.

Source: Stephens, 1981, based on Manton, 1977; Table III.

In Manton (1985) the earlier isotope studies were greatly extended and the results were reinterpreted. The recent study emphasized time changes in blood lead and in $^{206}Pb/^{207}Pb$ isotope ratios in three subjects in Dallas, Texas, from 1974 to 1983. Two of the subjects described earlier (Manton, 1977) were included here, a husband (subject 8) and his first wife (subject 9). The more recent subject was the husband's second wife. The husband had grown up in South Africa and in England; thus he had deep bone pools of lead that reflected the Australian lead isotope ratio. As noted earlier, the husband's seasonal minima in isotope ratio appeared to be the opposite of the two women with whom he shared a very similar pattern of environmental exposures. Manton (1985) now attributes this to a large efflux of lead from the skeletal pool. The husband's estimated dietary intake was 55 µg/day. If 10 percent of this is absorbed into blood (5.5 µg/day), mean residence time of 40 days and volume of distribution of 75 dl imply a dietary contribution to blood lead of about 3 µg/dl, much less than his observed average of 17 µg/dl. There was little indication of large changes in diet lead isotope ratio during this period, hence the changes in blood lead isotope ratio may be attributed to changes in the air lead particulate isotope ratio, and to changes in isotope ratio for endogenous sources. Manton attributes the large changes in isotope ratio in the husband to changes in isotope ratio from lead resorbed from bone into the blood. His estimate is that approximately 70 percent of the daily blood input is due to the endogenous skeletal pool of this subject. The subject's wife also exhibited a variety of fluctuations in blood lead level and isotope ratio due to childbirth and to short-term fluctuations in dietary lead. The apparent effect of childbirth was to increase resorption of both skeletal calcium and skeletal lead into blood. The contribution of airborne lead to blood lead isotope ratios thus did not require correction for long-term secular changes in dietary lead isotope ratios. On this basis the direct inhalation contribution was again calculated as about 20 to 60 percent of the total uptake of atmospheric lead using $\beta = 4.1$. Manton's calculations are shown in Table 11-19. The cumulative effects of long-term lead absorption on the mobilizable lead pool in the skeleton have been ignored, but are apparently not negligible.

In summary, the direct inhalation pathway accounts for only a fraction of the total air lead contribution to blood, the direct inhalation contribution being on the order of 12-23 percent of the total uptake of lead attributable to gasoline, using Stephen's assumptions, and 20-60 percent based on Manton's analysis. This is consistent with estimates from the ILE study, taking into account the much higher air lead levels in Turin.

11.3.6.3 Studies of Childhood Blood Lead Poisoning Control Programs. Billick et al. (1979) presented several possible explanations for the observed decline (described in Section 11.3.5.2) in blood lead levels in New York City children as well as evidence supporting and refuting each. The suggested contributing factors include the active educational and screening program of the New York City Bureau of Lead Poisoning Control, the decrease in the amount of lead-based paint exposure as a result of rehabilitation or removal of older housing, and changes in environmental lead exposure.

TABLE 11-19. RESPIRED AND OTHER INPUTS OF AIRBORNE Pb TO BLOOD FOR SOME DALLAS RESIDENTS IN 1975[a]

Subject no.	Blood Pb, μg/dl	Total Pb input, μg/day	Percent airborne Pb in blood	Total input airborne Pb, μg/day	Airborne Pb, 24-hr concentration, μg/m³	β^b	Airborne Pb		
							Respired μg/day	other, μg/day	Respired / Respired & other, %
3	8.4	15	31	4.5	0.22	12	0.91	3.6	20
6	12.6	30	39	11.7	1.09	4.5	4.5	7.2	38
8	5.5	9.3	>33	>3.1	0.45[c]	>4.1	1.9	>1.2	>61
9	17.4	45	20	9.0	0.45	7.7	1.9	7.1	21

[a] Data in first five columns for subjects 3, 6, and 9 recalculated.

[b] β is defined as the increment in blood Pb concentration (μg/dl) per unit increment in airborne Pb concentration (μg/m³).

[c] Fraction of airborne Pb in subject 8 calculated from measured isotope ratios of air, blood, and diet on two occasions in 1976. Figures quoted are minima because skeletal input, which would have had an isotope ratio less than that of the diet, has been ignored.

Information was only available to partially evaluate the last source of lead exposure and particularly only for ambient air lead levels. Air lead measurements were available during the entire study period for only one station which was located on the west side of Manhattan at a height of 56 m. Superposition of the air lead and blood lead levels indicated a similarity in seasonal cycle and long-term decline. The authors cautioned against overinterpretation because of the necessary assumptions in this analysis and because one air monitoring site was used to be representative of the air lead exposure of New York City residents. With this in mind, the investigators fitted a multiple regression model to the data to try to define the important determinants of blood lead levels for this population. Age, ethnic group, and air lead level were all found to be significant determinants of blood lead levels. The authors further point out the possibility of a change in the nature of the population being screened before and after 1973. They reran this regression analysis separately for years both before and after 1973. The same results were still obtained, although the exact coefficients varied.

Billick et al. (1980) extended their previous analysis of the data from the single monitoring site mentioned above. The investigators examined the possible relationship between blood lead level and the amount of lead in gasoline used in the area. Figures 11-14 and 11-15 present illustrative trend lines in blood leads for blacks and Hispanics versus air lead and gasoline lead, respectively. Gasoline lead was estimated by multiplying the sales of gasoline by the estimated concentrations of lead in gasoline. Semiannual concentrations of lead for the Mid-Atlantic Coast were interpolated to get quarterly values. Sales were computed using figures for New York, New York plus New Jersey, New York plus Connecticut, or New York plus New Jersey plus Connecticut: all gave similar results. The lead in gasoline trend line appears to fit the blood lead trend line better than the air lead trend, especially in the summer of 1973.

Multiple regression analyses were calculated using six separate models. The best fitting model had an $R^2 = 0.745$. Gasoline lead content was included rather than air lead. The gasoline lead content coefficient was significant for all three racial groups. Partial correlations with gasoline alone were not provided. The authors state a number of reasons for gasoline lead providing a better fit than air lead, including the fact that the single monitoring site might not be representative.

Nathanson and Nudelman (1980) provide more detail regarding air lead levels in New York City. In 1971, New York City began to regulate the lead content of gasoline sold. Lead in gasoline was to be totally banned by 1974, but supply and distribution problems delayed the effect of the ban. Ultimately, regulation of lead in gasoline was taken over by the U.S. Environmental Protection Agency.

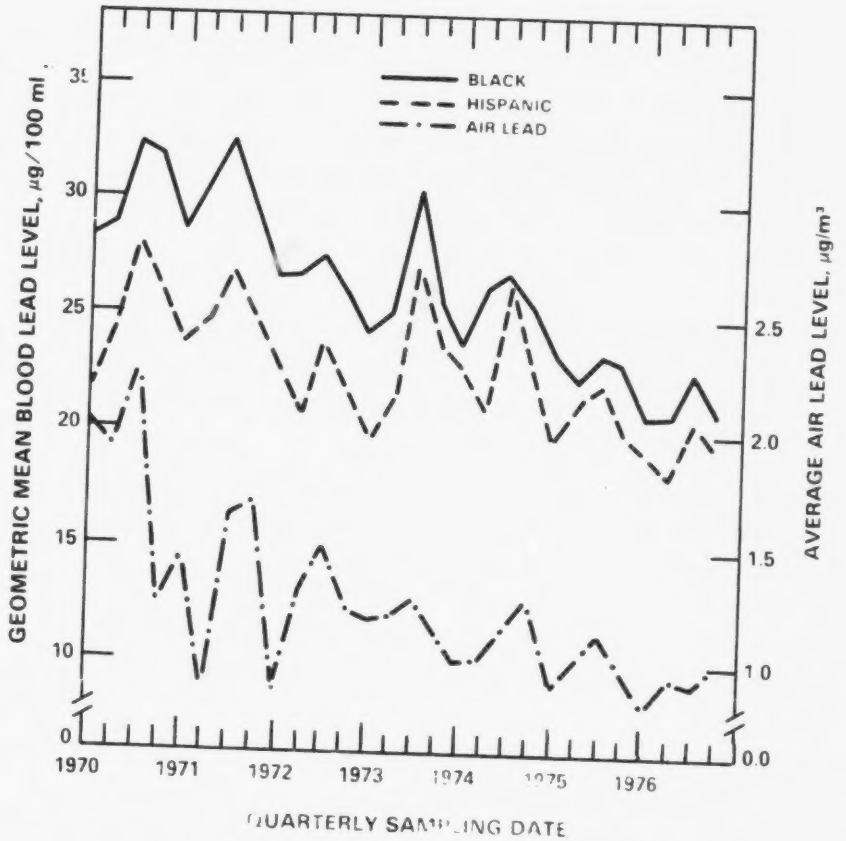


Figure 11-14. Geometric mean blood lead levels of New York City children (aged 25-36 months) by ethnic group, and ambient air lead concentration versus quarterly sampling period, 1970-1976.

Source: Billick et al. (1980).

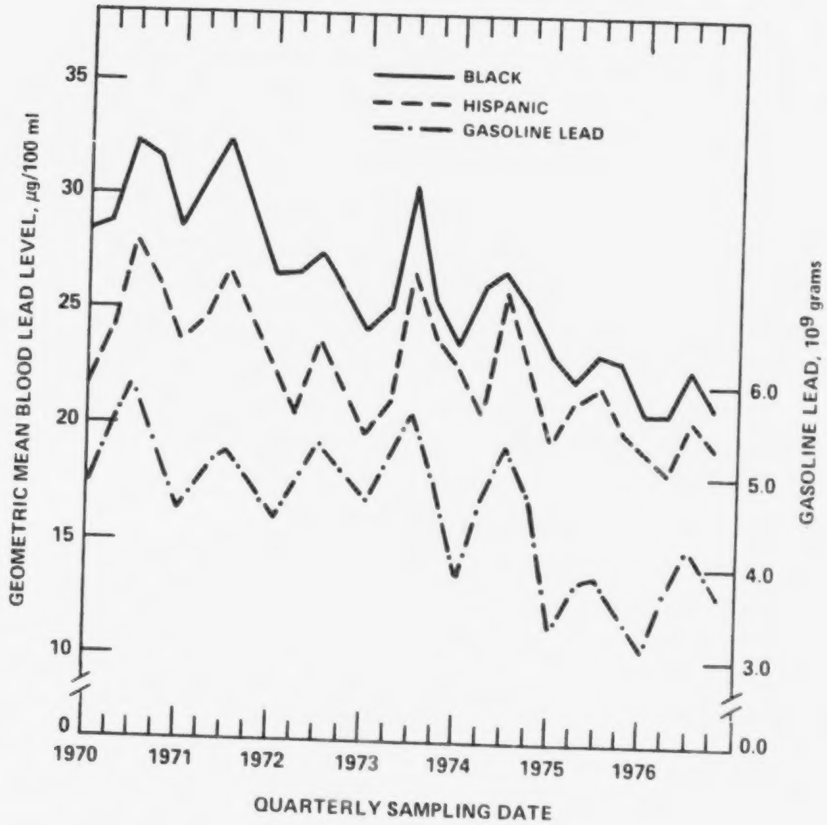


Figure 11-15. Geometric mean blood lead levels of New York City children (aged 25-36 months) by ethnic group, and estimated amount of lead present in gasoline sold in New York, New Jersey, and Connecticut versus quarterly sampling period, 1970-1976.

Source: Billick et al. (1980).

New York City measured air lead levels during the periods June 1969 to September 1973 and during 1978 at multiple sites. The earlier monitoring was done by 40 rooftop samplers using cellulose filters analyzed by AAS. The latter sampling was done by 27 rooftop samplers using glass fiber filters analyzed by X-ray fluorescence (XRF). There was excellent agreement between the XRF and atomic absorption analyses for lead ($r = 0.985$). Furthermore, the XRF analyses were checked against EPA AAS and again excellent agreement was found. The authors did, however, point out that cellulose filters are not as efficient as glass fiber filters. Therefore, the earlier results tend to be underestimates of air lead levels.

Quarterly citywide air lead averages generally declined during the years 1969-1978. The maximum quarterly citywide average obtained was about 2.5 $\mu g/m^3$ for the third quarter of 1970. The citywide trend corresponds to the results obtained from the single monitoring site used in Billick et al.'s (1979) analysis. The citywide data suggest that the single monitoring site in Manhattan is a responsible indicator of air lead level trends. The graph in Figure 11-16 reinforces this assertion by displaying the geometric mean blood lead levels for blacks and Hispanics in the 25- to 36-month age groups and the quarterly citywide air lead levels for the periods of interest. A good correspondence was noted.

As part of a detailed investigation of the relationship of blood lead levels and lead in gasoline covering three cities, Billick (1982) extended the time trend analyses of New York City blood lead data. Figure 11-17 presents the time trend line for geometric mean blood leads for blacks aged 25-36 months extended to 1979. Similar results held for other ages. The downward trend noted earlier was still continuing, although the slopes for both the blood and gasoline lead seem to be somewhat shallower toward the most recent data. A similar picture is presented by the percentage of children with blood lead levels greater than 30 µg/dl. In the early 70's, about 60 percent of the screened children had these levels; by 1979 the percentage had dropped between 10 and 15 percent.

11.3.6.4 Frankfurt, West Germany. Sinn (1980; 1981) conducted a study specifically examining the environmental and biological impact of the gasoline lead phasedown implemented in West Germany on January 1, 1976. Frankfurt am Main provided a good setting for such a study because of its physical character.

Air and dustfall lead levels at several sites in and about the city were determined before and after the phasedown was implemented. The mean air lead concentrations obtained during the study are presented in Table 11-20. A substantial decrease in air lead levels was noted for the low-level high traffic site (3.18 $\mu g/m^3$ in 1975-76 to 0.68 $\mu g/m^3$ in 1978-1979). No change was noted for the background site while only minor changes were observed for the other locations. Dustfall levels fell markedly (218 $mg/cm^2 \cdot day$ for 1972-1973 to 128 $mg/cm^2 \cdot day$ for 1977-1978). Traffic counts were essentially unchanged in the area during the course of study.

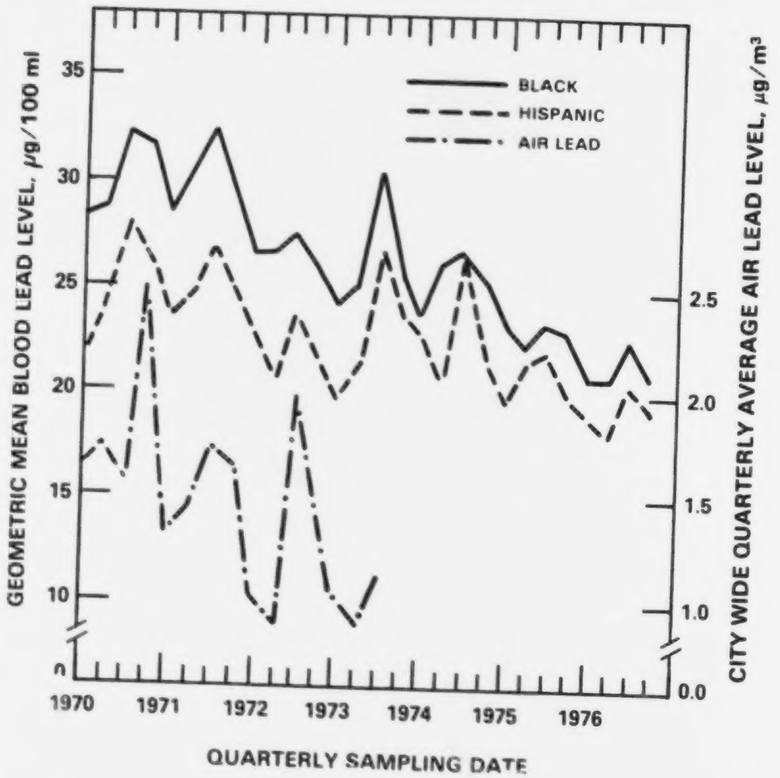


Figure 11-16. Geometric mean blood levels for blacks and Hispanics in the 25-to-36-month age group and rooftop quarterly averages for ambient citywide lead levels.

Source: Nathanson and Nudelman (1980).

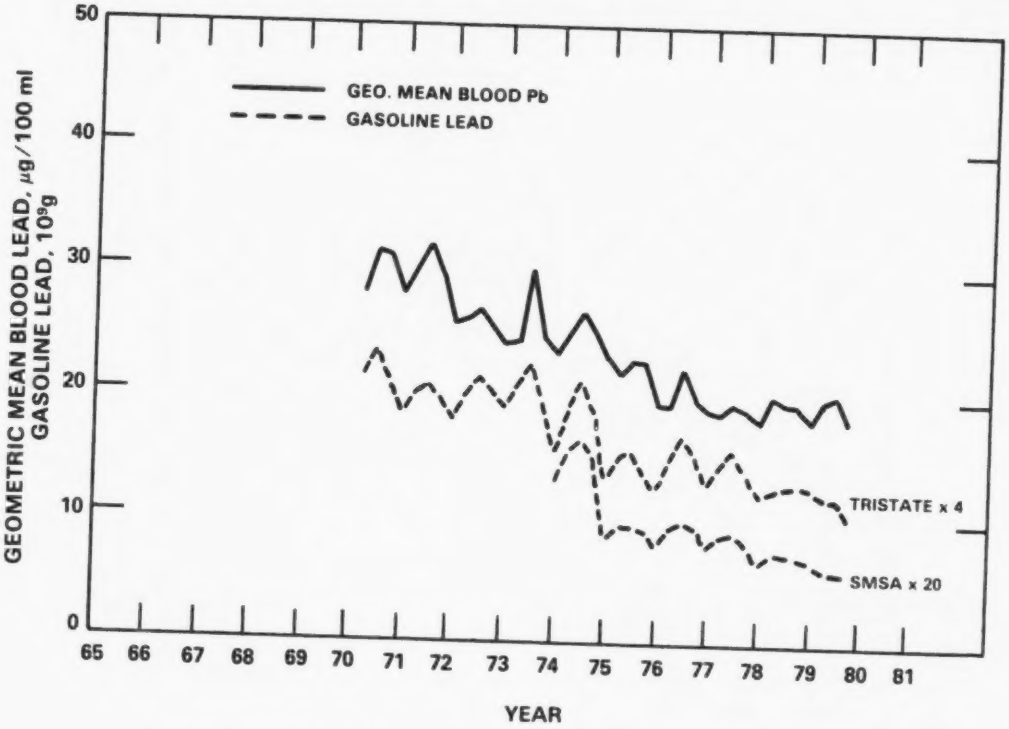


Figure 11-17. Time-dependence of blood lead and gas lead for blacks, aged 25 to 36 months, in New York.

Source: Billick (1982).

TABLE 11-20. MEAN AIR LEAD CONCENTRATIONS DURING THE VARIOUS BLOOD SAMPLING PERIODS AT THE MEASUREMENT SITES DESCRIBED IN THE TEXT ($\mu g/m^3$)

	Residential low traffic	High traffic (>20m)	High traffic (3m)	Background site
1975-1976	0.57	0.59	3.18	0.12
1976-1977	0.39	0.38	1.04	0.09
1977-1978	0.32	0.31	0.66	0.10
1978-1979	0.39	0.31	0.68	0.12

Source: Sinn (1980, 1981).

A number of population groups were included in the study of the blood lead levels; they were selected for having either occupational or residential exposure to high density automobile traffic. Blood samples were taken serially throughout the study (three phases in December-January 1975-1976, December-January 1976-1977, and December-January 1977-1978). Blood samples were collected by venipuncture and analyzed by three different laboratories. All the labs used AAS although sample preparation procedures varied. A quality control program across the laboratories was conducted. Due to differences in laboratory analyses, attrition, and loss of sample, the number of subjects who could be examined throughout the study was considerably reduced from the initial number recruited (124 out of 300).

Preliminary analyses indicated that the various categories of subjects had different blood lead levels, and that males and females within the same category differed. A very complicated series of analyses then ensued that made it difficult to draw conclusions because the various years' results were displayed separately by each laboratory performing the chemical analysis and by different groupings by sex and category. In Sinn's later report (1981), a downward trend was shown to exist for males and females who were in all years of the study and whose blood levels were analyzed by the same laboratory.

11.4 STUDIES RELATING EXTERNAL DOSE TO INTERNAL EXPOSURE

The purpose of this section is to assess the importance of environmental exposures in determining the level of lead in human populations. Of prime interest are those studies that yield quantitative estimates of the relationship between air lead exposures and blood lead levels. Related to this question is the evaluation of which environmental sources of airborne lead play a significant role in determining the overall impact of air lead exposures on blood lead levels.

A factor that complicates the analysis presented here is that lead does not remain suspended in the atmosphere but rather falls to the ground, is incorporated into soil, dust, and water, and enters the food chain over time (see Figure 11-1). Since man is exposed to lead from all of these media, as will be demonstrated below, studies that relate air lead levels to blood lead levels (especially experimental exposure studies) may underestimate the overall impact of airborne lead on blood lead levels. In observational studies, on the other hand, the effects of air lead will thus be confounded with lead exposures from other pathways. The simultaneous presence of lead in multiple environmental media requires the use of multiple variable analysis techniques or surrogate assessment of all other external exposures. Virtually no assessments of simultaneous exposures to all media have been done.

There are several key features that characterize good studies relating external exposure to internal exposure of lead:

(1) The study population is well-defined.
(2) There is a good measure of the exposure of each individual.
(3) The response variable (blood lead) is measured with adequate quality control, preferably with replicates.
(4) The statistical analysis model is biologically plausible and is consistent with the data.
(5) The important covariates are either controlled for or measured.

Some studies of considerable importance do not address all of these factors adequately. Key studies selected for discussion here are those which address enough of these factors sufficiently well to establish meaningful relationships.

The choice of the statistical analysis model is important in determining these relationships (for a more detailed discussion see Appendix 11B). The model used is especially critical in situations where lead is present in relatively low concentrations in one or more environmental media. A large number of statistical models have been used to predict blood lead from various environmental media. For simplicity, let PbB = blood lead, E_j = environmental exposure from source j, and b_j = the regression coefficient for source j. Using this notation, the more common models can be written as follows:

Linear Model: $\text{PbB} = b_0 + b_1 E_1 + \ldots + b_s E_s + \text{"error"}$ (11-2)

Linear Model (log form): $\log(\text{PbB}) = \log(b_0 + b_1 E_1 + \ldots + b_s E_s) + \text{"error"}$ (11-3)

Log-log Model: $\log(\text{PbB}) = \log(b_0) + b_1 \log(E_1) + \ldots + b_s \log(E_s) + \text{"error"}$ (11-4)

Log Total Exposure Model: $\log(\text{PbB}) = b \log(b_0 + b_1 E_1 + \ldots + b_s E_s) + \text{"error"}$ (11-5)

Power-Function Model: $$PbB = b_0 + (b_1 E_1 + \ldots + b_s E_s)^c + \text{"error"} \tag{11-6}$$

Cube-root Model: $$PbB = b_0 + b_1 (E_1)^{1/3} + \text{"error"} \tag{11-7}$$

There is no question that the relationship between blood lead and environmental exposure is nonlinear across the entire range of potential exposures, from very low to high levels. At lower levels of exposure, however, the various models all provide adequate descriptions of the observed data. The choice of a model must be based at least in part on the biological mechanisms. At the very least, no model should be adopted which is inconsistent with biological reality.

The compartment-type metabolic models described in Section 10.3.4 predict a linear response to total lead intake. Compartment models are described by a system of coupled first-order linear differential equations for the quantity of lead in various kinetically distinct body pools. (see Appendix 11-A). These compartments or kinetic pools may or may not correspond to distinct physiological systems. It is well known that if the kinetic rate coefficients and absorption coefficients in such a model are constant, then the equilibrium blood lead in a steady-intake environment is

$$PbB = \frac{\text{(lead absorbed into blood, µg/d) (Pb mean residence time in blood, d)}}{\text{(PbB volume of distribution, dl)}} \tag{11-8}$$

The only allowable places for nonlinearity in intake are either in the absorption process, or in the kinetics of lead distribution affecting the residence time. Nonlinearities affecting distribution volume are less plausible. Some of the evidence relating to these mechanisms was reviewed in Chapter 10. Chamberlain (1983) and U.S. EPA (1983) have concluded that after several months of steady exposure to environmental lead, blood lead levels achieve a near-equilibrium concentration that increases linearly with the ambient concentration no matter what the exposure pathway (directly by air inhalation, or by ingestion of food, water, dust, soil, or paint), provided the total exposure does not cause blood lead to exceed 30-40 µg/dl. However, when total lead exposure by any pathway becomes so great that blood lead levels greatly exceed 60-80 µg/dl, then the blood lead concentrations increase much more slowly with increasing exposure concentration than they did at lower levels.

On the other hand, the log-log and cube root models have slopes which approach infinity as the exposure approaches zero. The curves are so highly nonlinear at low doses that the models attribute nearly all of the increase of blood lead levels to the lowest exposures, and attribute relatively little increase to any additional exposures. However, the data of

Piomelli et al. (1980) on a population of Nepalese exposed to an air lead of 0.00086 µg/m³ had a geometric mean blood lead level of 3.4 µg/dl. This is similar to the value predicted by the log-log model of Goldsmith-Hexter.

The following sections give the models as presented by the original authors. In many cases, EPA has fitted other models in order to show the sensitivity of analysis to the model selected.

11.4.1 Air Studies

The studies emphasized in this section are those most relevant to answering the following question: If there is moderate change in average ambient air lead concentrations due to changes in environmental exposure (at or near existing EPA air lead standards), what changes are expected in blood lead levels of individual adults and children in the population? Longitudinal studies in which changes in blood lead can be measured in single individuals as responses to changes in air lead are discussed first. The cross-sectional relationship between blood lead and air lead levels in an exposed population provides a useful but different kind of information, since the population "snapshot" at some point in time does not directly measure changes in blood lead levels or responses to changes in air lead exposure. In this chapter consideration is also restricted to those individuals without known excessive occupational or personal exposures (except, perhaps, for some children in the Kellogg/Silver Valley study).

The previously published analyses of relevant studies have not agreed on a single form for the relationship between air lead and blood lead. All of the experimental studies have at least partial individual air lead exposure measures, as does the cross-sectional observational study of Azar et al. (1975). The 1974 Kellogg/Silver Valley study (Yankel et al., 1977) has also been analyzed using several models. Other population cross-sectional studies have been analyzed by Snee (1981). The most convenient method for summarizing these diverse studies and their several analyses is by use of the blood lead - air lead slope (β), where β measures the change in blood lead that is expected for a unit change in air lead. If determined for individual subjects in a study population, this slope is denoted β_i. If the fitted equation is linear, then β or β_i is the slope of the straight line relationship at any air lead level. If the fitted relationship is nonlinear, then the slope of the relationship measures the expected effect on blood lead of a small change in air lead at some given air lead value and thus will be somewhat different at different air lead levels.

A basic assumption here is that the distribution of blood lead in human populations with homogeneous exposure (same geometric mean blood lead) is lognormal; a second assumption is that all such lognormal distributions have the same geometric standard deviation (g.s.d.) or coefficient of variation (c.v.) It is then possible to calculate the fraction of the population in excess of any specific level of blood lead. Most subpopulations not occupationally exposed to lead have geometric mean blood lead < 20 µg/dl, at which level the effects of a few µg/dl change in blood lead can be well approximated by a linear function. On the other hand, many important experimental studies involve subjects with much higher blood lead. The response relationships derived from lead-exposed subjects (blood lead > 30 µg/dl) usually show much lower slopes b_j when blood lead exceeds 40 µg/dl. These two uses of blood lead versus intake models -- to predict the fraction of an exposed population at risk and to predict the change in blood lead of subjects exceeding a criterion blood lead level when blood lead exposure changes -- may require different blood lead slopes b_j. These two uses are not necessarily inconsistent, e.g., if there was a corresponding increase in biological variability of response to high levels of intake offsetting the decreased slope. For this reason we separately analyze the single-subject and population studies.

11.4.1.1 The Griffin et al. Study. The study of Griffin et al. (1975) has the largest number of human subjects exposed to atmospheric particulate lead at near-ambient conditions, under conditions of long-term controlled exposure. In two separate experiments conducted at the Clinton Correctional Facility in 1971 and 1972, adult male prisoner volunteers were sequestered in a prison hospital unit and exposed to approximately constant levels of lead oxide (average 10.9 µg/m^3 in the first study and 3.2 µg/m^3 in the second). Volunteers were exposed in an exposure chamber to an aerosol of submicron-sized particles of lead oxide, which was prepared by burning tetra-ethyl lead in a propane flame. There was an approximate additional 10-15 percent exposure to ambient organic lead vapor. All volunteers were introduced into the chamber 2 weeks before the initiation of the exposure; the lead exposures were scheduled to last 16 weeks, although the volunteers could drop out whenever they wished. Twenty-four volunteers, including 6 controls, participated in the 10.9 µg/m^3 exposure study. Not all volunteers completed the exposure regimen. Blood lead levels were found to stabilize after approximately 12 weeks. Among 8 men exposed to 10.9 µg/m^3 for at least 60 days, a stabilized mean level of 34.5 ± 5.1 µg/dl blood was obtained as compared with an initial level of 19.4 ± 3.3 µg/dl. All but two of the 13 men exposed at 3.2 µg/m^3 for at least 60 days showed increases and an overall stabilized level of 25.6 ± 3.9 µg/dl was found, compared with an initial level of 20.5 ± 4.4 µg/dl. This represented an increase of about 25 percent above the base level.

The aerosols used in this experiment were somewhat less complex chemically, as well as somewhat smaller, than those found in the ambient environment. The particle size obtained was 0.05-0.10 µm, which is smaller than true urban aerosol of 0.3 µm. Griffin et al. (1975), however, pointed out that good agreement was achieved on the basis of the comparison of their observed blood lead levels with those predicted by Goldsmith and Hexter's (1967) equation; that is, $\log_{10}$ blood lead = 1.265 + 0.2433 $\log_{10}$ atmospheric air lead. The average diet content of lead was measured and blood lead levels were observed at 1- or 2-week intervals for several months. Eight subjects received the maximum 4-month exposure to 10.9 μg/m^3; nine subjects were exposed for 1 - 3 months. Six subjects had the maximum 4-month exposure to 3.2 μg/m^3, and eight others had shorter exposures.

Compartmental models have been fitted to these data by O'Flaherty et al. (1982) and by EPA. The basis of these models is that the mass of lead in each of several distinct pools or compartments within the body changes according to a system of coupled first-order linear differential equations with constant fractional transfer rates (Batschelet et al., 1979; Rabinowitz et al., 1976). Such a model predicts that when the lead intake changes from one constant level to another, then the relationship between the mass of lead in each compartment and time with constant intake has a single exponential term.

The subjects at 3.2 μg/m^3 exhibited a smaller increase in blood lead, with correspondingly less accurate estimates of the parameters. Several of the lead-exposed subjects failed to show an increase.

EPA has reanalyzed these data using a two-compartment model for two reasons:

(1) Semilogarithmic plots of blood lead versus time for most subjects showed a two-component exponential decrease of blood lead during the postexposure or washout phase of the experiments. Rabinowitz et al. (1977) show that at least two pools are necessary to model blood lead kinetics accurately. The first pool is tentatively identified with blood and the most labile soft tissues. The second pool probably includes soft tissues and labile bone pools.

(2) Kinetic models are needed to account for the subjects' lead burdens not being in equilibrium at any phase of the experiments.

Previously published analyses have not used data for all 43 subjects, particularly for the same six subjects (labeled 15-20 in both experiments) who served as controls both years. These subjects establish a baseline for non-inhalation exposures to lead, e.g., in diet and water, and allow an independent assessment of within-subject variability over time. EPA analyzed data for these subjects as well as others who received lead exposures of shorter duration.

The estimated blood lead inhalation slope, β, was calculated for each individual subject according to the formula

$$\beta = \frac{(\text{Change in intake, } \mu\text{g/day}) \times (\text{mean residence time in blood, day})}{(\text{Change in air exposure, } \mu\text{g/m}^3) \times (\text{Volume of distribution, dl})} \qquad (11\text{-}9)$$

The changes in air exposure were 10.9-0.15 = 10.75 μg/m³ for 1970-71 and 3.2-0.15 = 3.05 μg/m³ in 1971-72. Paired sample t-tests of equal means were carried out for the six controls and five subjects with exposure both years, and independent sample t-tests were carried out comparing the remaining 12 subjects the first year and nine different subjects the next year. All standard error estimates include within-subject parameter estimation uncertainties as well as between subject differences. The following are observations:

(1) Non-inhalation lead intake of the control subjects varied substantially during the second experiment at 3.2 μg/m³, with clear indication of low intake during the 14-day pre-exposure period (resulting in a net decrease of blood lead). There was an increase in lead intake (resulting in either equilibrium or net increase of blood lead) during the exposure period. Subjects 16 and 20 had substantial increases, subjects 15 and 19 had moderate increases, and subject 18 had no increase in blood lead during exposure. Subject 17 had a marked decline in blood lead, but the rate of decrease was much faster in the pre-exposure period, suggesting an apparent increase of intake during exposure periods even for this subject. These subjects had not apparently achieved equilibrium in either blood or tissue compartments. Even though these subjects were not exposed to air lead, the estimated difference between blood lead intake before and during exposure of the other subjects was used to calculate the apparent inhalation slope at that exposure. The pooled inhalation slope estimated for all six controls (1.48 ± 0.82 s.e.) was significantly positive ($Z = 1.76$, one-tailed $p < 0.05$), as shown in Table 11-21. No explanation for the increased lead intake during the winter of 1971-72 can be advanced at this time, but factors such as changes in diet or changes in resorption of bone lead are likely to have had an equal effect on the lead-exposed subjects. No statistically significant changes in the controls were found during the first experiment at 10.9 μg/m³.

(2) Among the controls, the estimated mean residence time in blood was slightly longer for the first year than the second year, 41.8 ± 9.2 days versus 34.6 ± 6.5 days, but a paired sample Z-test found that the mean difference for the controls (7.2 ± 11.2 days) was not significantly different from zero (see Table 11-22).

(3) Among the five subjects exposed to 10.9 μg/m³ the first year and 3.2 μg/m³ the second year, the mean residence time in blood was almost identical (43.9 ± 9.4 versus 44.7 ± 8.7 days).

TABLE 11-21. GRIFFIN ET AL. (1975) EXPERIMENT INHALATION SLOPE ESTIMATES

Group	At 3.2 $\mu g/m^3$	At 10.9 $\mu g/m^3$
Controls	1.48 ± 0.82 (n = 6)*	-0.20 ± 0.27 (n = 6)
All exposed	3.00 ± 0.76 (n = 14)	1.57 ± 0.26 (n = 17)
Difference (Exposed controls)	1.52 ± 1.12	1.77 ± 0.37
Pooled: (all subjects)	1.75 ± 0.35	
(without subjects 1,6)**	1.78 ± 0.35	

*n = number of subjects.
**Subjects 1 and 6 were "non-responders."

TABLE 11-22. GRIFFIN ET AL. (1975) EXPERIMENT MEAN RESIDENCE TIME IN BLOOD

	3.2 $\mu g/m^3$ experiment	10.9 $\mu g/m^3$ experiment
Control	34.6 ± 6.5 days	41.8 ± 9.2 days
Exposed	40.8 ± 4.4 days	40.6 ± 3.6 days

(4) The average inhalation slope for all 17 subjects exposed to 10.9 $\mu g/m^3$ is 1.77 ± 0.37 when the slope for the controls is subtracted. The corrected inhalation slope for all 14 subjects exposed to 3.2 $\mu g/m^3$ is 1.52 ± 1.12, or 1.90 ± 1.14 without subjects 1 and 6 who were "non-responders." These are not significantly different. The pooled slope estimate for all subjects is 1.75 ± 0.35. The pooled mean residence time for all subjects is 39.9 ± 2.5 days.

Thus, in spite of the large estimation variability at the lower exposure level, the average inhalation slope estimate and blood lead half-life are not significantly different at the two exposure levels. This suggests that blood lead response to small changes in air lead inhalation is approximately linear at typical ambient levels.

11.4.1.2 The Rabinowitz et al. Study. The use of stable lead isotopes avoids many of the difficulties encountered in the analysis of whole blood lead levels in experimental studies. Five adult male volunteers were housed in the metabolic research wards of the Sepulveda and Wadsworth VA hospitals in Los Angeles for extended periods (Rabinowitz et al., 1974; 1976; 1977). For much of the time they were given low-lead diets with controlled lead content, supplemented by tracer lead salts at different times.

Four subjects were initially observed in the ward for several weeks. Each subject was in the semi-controlled ward about 14 hours per day and was allowed outside for 10 hours per day, allowing the blood lead concentration to stabilize.

Subjects B, D, and E then spent 22-24 hours per day for 40, 25, and 50 days, respectively, in a low-lead room with total particulate and vapor lead concentrations that were much lower than in the metabolic wards or outside (see Table 11-23). The subjects were thereafter exposed to Los Angeles air with much higher air lead concentrations than in the ward.

The calculated changes in lead intake upon entering and leaving the low-lead chamber are shown in Table 11-24. These were based on the assumption that the change in total blood lead was proportional to the change in daily lead intake. The change in calculated air lead intakes (other than cigarettes) due to removal to the clean room were also calculated independently by the lead balance and labeled tracer methods (Rabinowitz et al., 1976) and are consistent with these direct estimates.

Rabinowitz and coworkers assumed that the amount of lead in compartments within the body evolved as a coupled system of first-order linear differential equations with constant fractional transfer rates. This compartmental model was fitted to the data. This method of analysis is described in Appendix 11A.

Blood lead levels calculated from the three compartment model adequately predicted the observed blood lead levels over periods of several hundred days. There was no evidence to suggest homeostasis or other mechanisms of lead metabolism not included in the model. There was some indication (Rabinowitz et al., 1976) that gut absorption may vary from time to time.

The calculated volumes of the pool with blood lead (Table 11-24) are much larger than the body mass of blood (about 7 percent of body weight, estimated respectively as 4.9, 6.3, 6.3, 4.6, and 6.3 kg for subjects A-E). The blood lead compartment must include a substantial mass of other tissue.

The mean residence time in blood in Table 11-24 includes both loss of lead from blood to urine and transfer of a fraction of blood lead to other tissue pools. This parameter reflects the speed with which blood lead concentrations approach a new quasi-equilibrium level. Many years may be needed before approaching a genuine equilibrium level that includes lead that can be mobilized from bones.

TABLE 11-23. AIR LEAD CONCENTRATIONS* ($\mu g/m^3$) FOR TWO SUBJECTS IN THE RABINOWITZ STUDIES

	Environment	Average	Range
Subject A	Outside (Sepulveda VA)	1.8	(1.2-2.4)
	Inside (Sepulveda VA, air-conditioned without filter)	1.5	(1.0-2.7)
	Inside (Wadsworth VA, Open air room)	2.1	(1.8-2.6)
Subject B	(Wadsworth VA)		
	Outside	2.0	(1.6-2.4)
	In room (air conditioner with filter, no purifier)	0.97	(0.4-2.1)
	In room (with purifiers, "clean air")	0.072	(0.062-0.087)
	Open-air room	1.9	(1.8-1.9)
	Organic vapor lead		
	Outside	0.10	-
	"Clean air"	0.05	-

* 5-20 days exposure for each particulate lead filter.

One of the greatest difficulties in using these experiments is that the air lead exposures of the subjects were not measured directly, either by personal monitors or by restricting the subjects to the metabolic wards. The times when the subjects were allowed outside the wards included possible exposures to ground floor and street level air, whereas the outside air lead monitor was mounted outside the third-floor window of the ward. The VA hospitals are not far from major streets and the subjects' street level exposures could have been much higher than those measured at about 10 m elevation (see Section 7.2.1.3). Some estimated ratios between air concentrations at elevated and street level sites are given in Table 7-6.

A second complication is that the inside ward value of $\mu g/m^3$ (Rabinowitz et al., 1977) used for subject B may be appropriate for the Wadsworth VA hospital, but not for subject A in the Sepulveda VA hospital (see Table 11-23). The changes in air lead values shown in Table 11-24 are thus nominal, and are likely to have systematic inaccuracies much larger than the

TABLE 11-24. ESTIMATES OF INHALATION SLOPE, β, FOR RABINOWITZ STUDIES

Subject	Changes in intake*, µg/day	Volume,** kg	Residence† time, days	Changes in air lead††, µg/m³	Inhalation+† slope, µg/dℓ per µg/m³	Maximum slope++
A	17 ± 5*	7.4 ± 0.6	34 ± 5	2.5††	2.98 ± 1.06	4.38 ± 1.55
B	16 ± 3	10.0 ± 0.8	40 ± 5	2.0	3.56 ± 0.93	5.88 ± 1.54
C	15 ± 5*	10.1 ± 1**	37 ± 5	2.2††	2.67 ± 1.04	4.16 ± 1.62
D	9 ± 2	9.9 ± 1.2	40 ± 5	2.0	2.02 ± 0.60	3.34 ± 0.99
E	12 ± 2	11.3 ± 1.4	27 ± 5	2.0	1.59 ± 0.47	2.63 ± 0.78

*From Rabinowitz et al. (1977), Table VI. Reduced intake by low-lead method for subjects B, D, E, tracer method for A, balance method for C. Standard error for C is assumed by EPA to be same as A.

**From Rabinowitz et al. (1976), Table II. EPA has assumed standard error with coefficient of variation same as that for quantity of tracer absorbed in Table VI, except for subject C.

†Estimates from Rabinowitz et al. (1976) Table II. Standard error estimate from combined sample.

††See text. For A and C, estimated from average exposure. For B, D, and E reduced by 0.2 µg/m³ for clean room exposure. Coefficient of variation assumed to be 10%.

+Assumed density of blood 1.058 g/cm³.

++Assuming outside air exposure is 2.1 µg/m³ rather than 4 µg/m³ for 10 hours.

nominal 10 percent coefficients of variation stated. The assumption is that for subjects B, D, and E, the exposure to street level air for 10 hours per day was twice as large as the measured roof level air, i.e., 4 µg/m³; and the remaining 14 hours per day were at the ward level of 0.97 µg/m³; thus the time-averaged level was [(10 x 4) + (14 x 0.97)]/24 = 2.23 µg/m³. The average controlled exposures during the "clean room" part of the experiment were 23, 22, and 24 hours respectively for subjects B, D, E; thus averaged exposures were 0.19, 0.28, and 0.12 µg/m³, and reductions in exposure were about 2.0 µg/m³. This value is used to calculate the slope. For subject A, the total intake due to respired air is the assumed indoor average of 1.5 µg/m³ for the Sepulveda VA hospital, combining indoor and outdoor levels [(10 x 4) + (14 x 1.5)]/24 = 2.54 µg/m³. For subject C the Wadsworth average applies. Other than uncertainties in the air lead concentration, the inhalation slope estimates for Rabinowitz's subjects have less internal uncertainty than those calculated for subjects in Griffin's experiment.

The inhalation slopes thus calculated are the lowest that can be reasonably derived from this experiment, since the largest plausible air lead concentrations have been assumed. The third-floor air monitor average of 2.1 μg/m^3 is a plausible minimum exposure, leading to the higher plausible maximum inhalation slopes in the last column of Table 11-24. These are based on the assumption that the time-averaged air lead exposure is smaller by $[10(4-2.1)]/24 = 0.79$ μg/m^3 than assumed previously. It is also possible that some of this difference can be attributed to dust ingestion while outside the metabolic ward.

11.4.1.3 The Chamberlain et al. Study. A series of investigations were carried out by Chamberlain et al. (1975a,b; 1978) at the U.K. Atomic Energy Research Establishment in Harwell, England. The studies included exposure of up to 10 volunteer subjects to inhaled, ingested, and injected lead in various physical forms. The inhalation exposures included laboratory inhalation of lead aerosols generated in a wind tunnel, or box, of various particle sizes and chemical compositions (lead oxide and lead nitrate). Venous blood samples were taken at several times after inhalation of ^{203}Pb. Three subjects also breathed natural highway exhaust fumes at various locations for times up to about 4.5 hours.

The natural respiratory cycles in the experiments varied from 5.7 to 17.6 seconds (4 to 11 breaths per minute) and tidal volumes from 1.6 to 2.3 liters. Lung deposition of lead-bearing particles depended strongly on particle size and composition, with natural exhaust particles being more efficiently retained by the lung (30 - 50 percent) than were the chemical compounds (20 - 40 percent).

The clearance of lead from the lungs was an extended process over time and depended on particle size and composition, leaving only about 1 percent of the fine wind tunnel aerosols in the lung after 100 hours, but about 10 percent of the carbonaceous exhaust aerosols. The ^{203}Pb isotope reached a peak blood level about 30 hours after inhalation, the blood level then representing about 60 percent of the initial lung burden.

A substantial fraction of the lead deposited in the lung appears to be unavailable to the blood pool in the short term, possibly due to rapid transport to and retention in other tissues including skeletal tissues. In long-term balance studies, some of this lead in the deep tissue compartment would return to the blood compartment.

Lead kinetics were also studied by use of injected and ingested tracers, which suggested that in the short term, the mean residence time of lead in blood could be calculated from a one-pool model analysis.

Chamberlain et al. (1978) extrapolated these high-level, short-term exposures to longer term ones. The following formula and data were used to calculate a blood-to-air level ratio

$$\beta = \frac{[T_{1/2}]\ [\%\ \text{Deposition}]\ [\%\ \text{Absorption}]\ [\text{Daily ventilation}]}{[\text{Blood volume}]\ [0.693]} \qquad (11\text{-}10)$$

where:

$T_{1/2}$ = biological half life

With an estimated value of $T_{1/2}$ = 18 days (mean residence time $T_{1/2}/0.693$ = 26 days), with 50 percent for deposition in lung for ordinary urban dwellers, and 55 percent of the lung lead retained in the blood lead compartment (all based on Chamberlain's experiments), with an assumed ventilation of 20 m^3/day over blood volume 5400 ml (Table 10-20 in Chamberlain et al., 1978), then

$$\beta = \frac{26 \text{ day} \times 0.50 \times 0.55 \times 20 \text{ m}^3/\text{day}}{54 \text{ dl}} = 2.7 \text{ m}^3/\text{dl} \qquad (11\text{-}11)$$

This value of β could vary for the following reasons:

1. The absorption from lung to blood used here, 0.55, refers to short-term kinetics. In the long term, little lead is lost through biliary or pancreatic secretions, nails, hair, and sweat, so that most of the body lead is available to the blood pool even if stored in the skeleton from which it may be resorbed. Chamberlain suggests an empirical correction to 0.55 X 1.3 = 0.715 absorption.

2. The mean residence time, 26 days, is shorter than in Rabinowitz's subjects, and the blood volume is less, 54 dl. It is possible that in the Rabinowitz study, the mean times are longer and the blood pool size (100 dl) is larger than here because Rabinowitz et al. included relatively fewer labile tissues such as kidney and liver in the pool. Assuming 40 days mean residence time and 100 dl blood volume the slope can be recalculated,

$$\beta = \frac{40 \text{ d} \times 0.50 \times 0.55 \times 20 \text{ m}^3/\text{d}}{100 \text{ dl}} = 2.2 \text{ m}^3/\text{dl}. \qquad (11\text{-}12)$$

3. The breathing rate could be much less, for inactive people.

11.4.1.4 The Kehoe Study. Between 1950 and 1971, Kehoe exposed 12 subjects to various levels of air lead under a wide variety of conditions. Four earlier subjects had received oral lead during 1937-45. The inhalation experiments were carried out in an inhalation chamber at the University of Cincinnati, in which the subjects spent varying daily time periods over extended intervals. The duration was typically 112 days for each exposure level in the inhalation studies, and at the end of this period it was assumed the blood lead concentration had reached a near-equilibrium level. The experiments are described by Kehoe (1961a,b,c) and the data and their analyses by Gross (1981) and Hammond et al. (1981). The studies most relevant to this document are those in which only particles of lead sesquioxide aerosols in the submicron range were used, so that there was at least one air lead exposure (other than control) for which the time-averaged air lead concentration did not exceed 10 µg/m^3. Only six subjects met these criteria: LD (1960-63), JOS (1960-63), NK (1963-66), SS (1963-68), HR (1966-67), and DH (1967-69). Subject DH had a rather high initial blood lead concentration (30 µg/dl) that fell during the course of the experiment to 28 µg/dl; apparently daily detention in the inhalation chamber altered DH's normal pattern of lead exposure to one of lesser total exposure. The Kehoe studies did not measure non-experimental airborne lead exposures, and did not measure lead exposures during "off" periods. Subject HR received three exposure levels from 2.4-7.5 µg/m^3, subject NK seven exposure levels from 0.6-4.2 µg/m^3, and subject SS 13 exposure levels from 0.6-7.2 µg/m^3. LD and JOS were each exposed to about 9, 19, 27, and 36 µg/m^3 during sequential periods of 109-113 days.

A great deal of data on lead content in blood, feces, urine and diet were obtained in these studies and are exhibited graphically in Gross (1979) (see Figure 11-18). Apart from the quasi-equilibrium blood lead values and balances reported in Gross (1979; 1981), there has been little use of these data to study the uptake and distribution kinetics of lead in man. EPA analyses used only the summary data in Gross (1981).

Data from Gross (1981) were fitted by least squares linear and quadratic regression models. The quadratic models were not significantly better than the linear model except for subjects LD and JOS, who were exposed to air levels above 10 µg/m^3. The linear terms predominate in all models for air lead concentrations below 10 µg/m^3 and are reported in Table 11-25. These data represent most of the available experimental evidence in the higher range of ambient exposure levels, approximately 3-10 µg/m^3. Data for the four subjects with statistically significant relationships are shown in Figure 11-19, along with the fitted regression curve and its 95 percent confidence band.

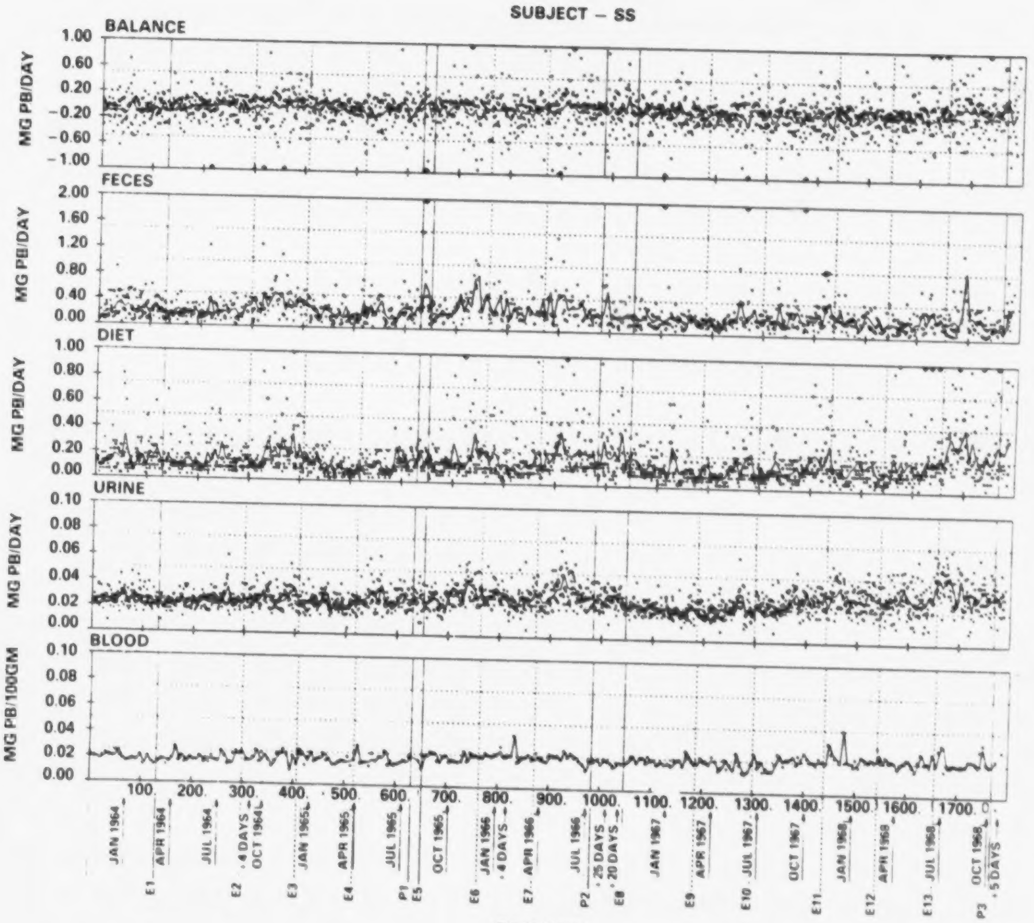


Figure 11-18. Data plots for individual subjects as a function of time for Kehoe subjects, as presented by Gross (1979).

TABLE 11-25. LINEAR SLOPE FOR BLOOD LEAD VERSUS AIR LEAD AT LOW AIR LEAD EXPOSURE IN KEHOE'S SUBJECTS

Subject	Linear Slopes β, m³/dl, ± s.e.		Range	
	Linear Model	Quadratic Model	Air*, μg/m³	Blood, μg/dℓ
DH[a]	-0.34 ± 0.28	0.14 ± 1.25	5.6 - 8.8	26 - 31
HR[a]	0.70 ± 0.46	0.20 ± 2.14	2.4 - 7.5	21 - 27
JOS[b]	0.67 ± 0.07	1.01 ± 0.19	9.4 - 35.7	21 - 46
LD[b]	0.64 ± 0.11	1.29 ± 0.06	9.3 - 35.9	18 - 41
NK[c]	2.60 ± 0.32	1.55 ± 1.28	0.6 - 4.0	20 - 30
SS[c]	1.31 ± 0.20	1.16 ± 0.78	0.6 - 7.2	18 - 29

*Also, control = 0.

[a] No statistically significant relationship between air and blood lead.

[b] High exposures. Use linear slope from quadratic model.

[c] Low exposures. Use linear slope from linear model.

11.4.1.5 The Azar et al. Study. Thirty adult male subjects were obtained from each of five groups: 1) Philadelphia cab drivers; 2) DuPont employees in Starke, Florida; 3) DuPont employees in Barksdale, Wisconsin; 4) Los Angeles cab drivers; and 5) Los Angeles office workers (Azar et al., 1975). Subjects carried air lead monitors in their automobiles and in their breathing zones at home and work. Personal variables (age, smoking habits, water samples) were obtained from all subjects, except for water samples from Philadelphia cab drivers. Blood lead, ALAD urine lead, and other variables were measured. From two to eight blood samples were obtained from each subject during the air monitoring phase. Blood lead determinations were done in duplicate. Table 11-26 presents the geometric means for air lead and blood lead for the five groups. The geometric means were calculated by EPA from the raw data presented in the authors' report (Azar et al., 1975).

The Azar study has played an important role in setting standards because of the care used in measuring air lead in the subjects' breathing zone. Blood lead levels change in response to air lead levels, with typical time constants of 20-60 days. One must assume that the subjects' lead exposures during preceding months had been reasonably similar to those during the study period. Models have been proposed for these data by Azar et al. (1975), Snee (1981; 1982b), and Hammond et al. (1981) including certain nonlinear models.

Azar et al. (1975) used a log-log model for their analysis of the data. The model included dummy variables, C_1, C_2, C_3, C_4, C_5, which take on the value 1 for subjects in that group and 0 otherwise (see Table 11-26 for the definitions of these dummy variables). The fitted model using natural logarithms was

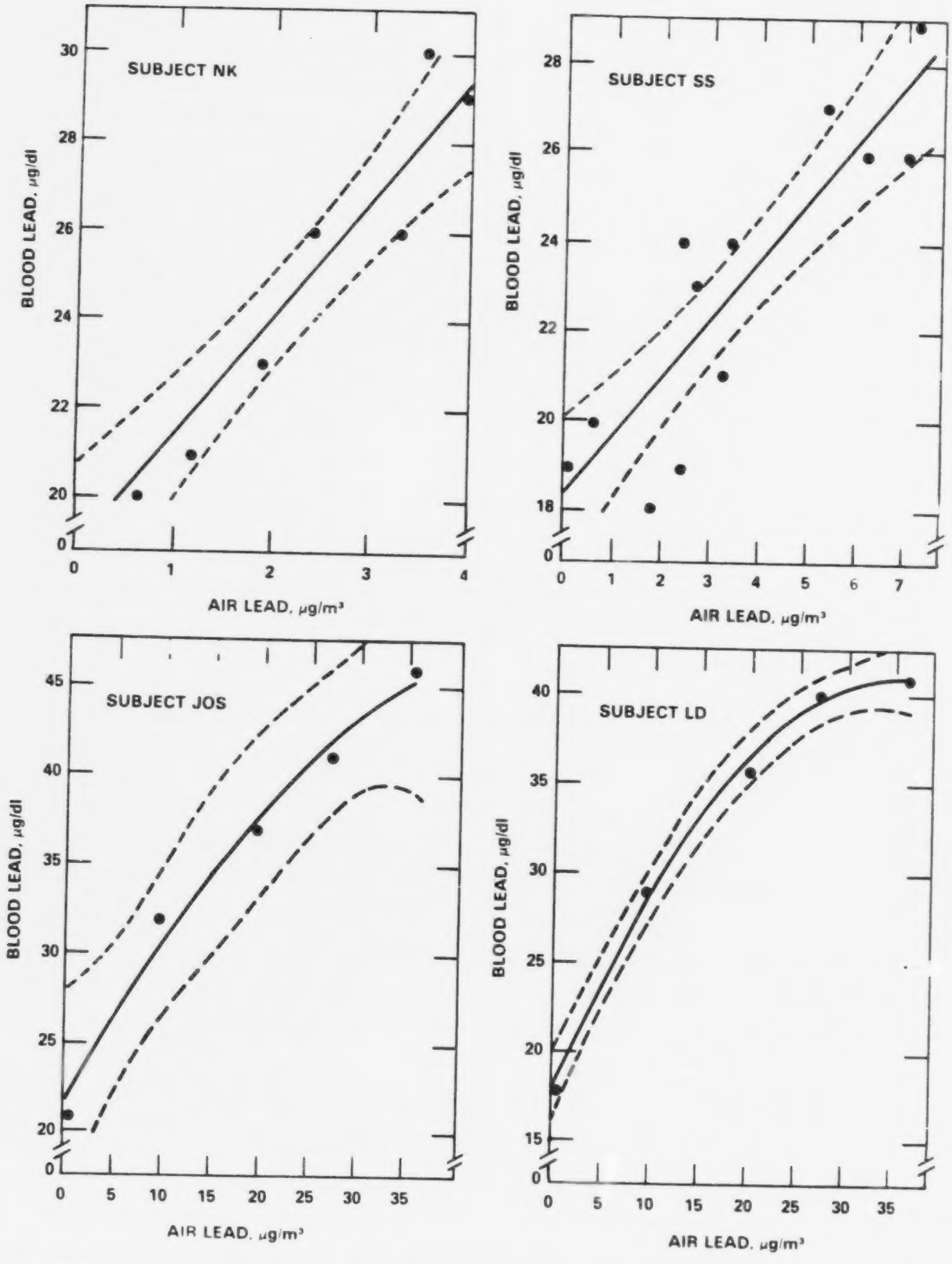


Figure 11-19. Blood level vs. air lead relationships for Kehoe inhalation studies: linear relation for low exposures, quadratic for high exposures, with 95% confidence bands.

TABLE 11-26. GEOMETRIC MEAN AIR AND BLOOD LEAD LEVELS (μg/100 g) FOR FIVE CITY-OCCUPATION GROUPS (DATA CALCULATED BY EPA)

Group	Geometric mean air lead, μg/m³	GSD	Geometric mean blood lead, μg/100 g	GSD	Sample size	Code
Cab drivers Philadelphia, PA	2.59	1.16	22.1	1.16	30	C_1
Plant employees Starke, FL	0.59	2.04	15.4	1.41	29	C_2
Plant employees Barksdale, WI	0.61	2.39	12.8	1.43	30	C_3
Cabdrivers Los Angeles, CA	6.02	1.18	24.2	1.20	30	C_4
Office workers Los Angeles, CA	2.97	1.29	18.4	1.24	30	C_5

Source: Azar et al. (1975).

$$\log(\text{blood Pb}) = 2.951\,C_1 + 2.818\,C_2 + 2.627\,C_3 + 2.910\,C_4 + 2.821\,C_5 + 0.153\log(\text{air Pb}) \qquad (11\text{-}13)$$

This model gave a residual sum of squares of 9.013, a mean square error of 0.063 (143 degrees of freedom), and a multiple R^2 of 0.502. The air lead coefficient had a standard error of 0.040. The fitted model is nonlinear on air lead, and so the slope depends on both air lead and the intercept. Using an average intercept value of 1.226, the curve has a slope ranging from 10.1 at an air lead level of 0.2 μg/m³ to 0.40 at an air lead level of 9 μg/m³.

Snee (1982b) reanalyzed the same data and fitted the following power function model,

$$\log(\text{blood Pb}) = \log[12.1\,(\text{air Pb} + 6.00\,C_1 + 1.46\,C_2 + 0.44\,C_3 + 2.23\,C_4 + 6.26\,C_5)^{0.2669}]$$

This model gave a residual sum of squares of 9.101, a mean square error of 0.063 (142 degrees of freedom) and a multiple R^2 of 0.497. Using an average constant value of 3.28, the slope ranges from 1.29 at an air lead of 0.2 to 0.51 at an air lead of 9.

An important extension in the development of models for the data was the inclusion of separate non-air contributions or background exposures for each separate group. The coefficients of the group variables, C_j, in the lead exposure model may be interpreted as measures of total exposure of that group to non-air external sources (cigarettes, food, dust, water) and to endogenous sources (lead stored in skeleton). Water and smoking variables were used to estimate some external sources. (This required deleting another observation for a subject with unusually high water lead.) The effect of endogenous lead was estimated using subject age as a surrogate measure of cumulative exposure, since lead stored in the skeleton is known to increase approximately linearly with age, for ages 20-60 (Gross et al., 1975; Barry, 1975; Steenhout, 1982) in homogeneous populations.

In order to facilitate comparison with the constant β ratios calculated from the clinical studies, EPA fitted a linear exposure model to the Azar data. The model was fitted on a logarithmic scale to facilitate comparison of goodness of fit with other exposure models and to produce an approximately normal pattern of regression residuals. Neither smoking nor water lead provided significantly better fits to the log (blood lead) measurements after the effect of age was removed.

Age and air lead may be confounded to some extent because the regression coefficient for age may include the effects of prior air lead exposures on skeletal lead buildup. This would have the effect of reducing the estimated apparent slope β.

Geometric mean regressions of blood lead on air lead were calculated by EPA for several assumptions: (1) A linear model analogous to Snee's exposure model, assuming different non-air contributions in blood lead for each of the five subgroups; (2) a linear model in which age of the subject is also used as a surrogate measure of the cumulative body burden of lead that provides an endogenous source of blood lead; (3) a linear model similar to (2), in which the change of blood lead with age is different in different subgroups, but it is assumed that the non-air contribution is the same in all five groups (as was assumed in the 1977 EPA Lead Criteria Document); (4) a linear model in which both the non-air background and the change in blood lead with age may differ by group; and (5) a nonlinear model similar to (4). None of the fitted models are significantly different from each other using statistical tests of hypotheses about parameter subsets in nonlinear regression (Gallant, 1975).

11.4.1.6 Silver Valley/Kellogg, Idaho Study. In 1970, EPA carried out a study of a lead smelter in Kellogg, Idaho (Hammer et al., 1972; U.S. Environmental Protection Agency, 1972). The study was part of a national effort to determine the effects of sulfur dioxide, total suspended particulate and suspended sulfates, singly and in combination with other pollutants, on human health. It focused on mixtures of the sulfur compounds and metals. Although it was demonstrated that children had evidence of lead absorption, insufficient environmental data were reported to allow further quantitative analyses.

In 1974, following the hospitalization of two children from Kellogg with suspected acute lead poisoning, the CDC joined the State of Idaho in a comprehensive study of children in the Silver Valley area of Shoshone County, Idaho, near the Kellogg smelter (Yankel et al., 1977; Landrigan et al., 1976).

The principal source of exposure was a smelter whose records showed that emissions averaged 8.3 metric tons per month from 1955 to 1964 and 11.7 metric tons from 1965 to September, 1973. After a September, 1973 fire extensively damaged the smelter's main emission filtration facility, emissions averaged 35.3 metric tons from October, 1973 to September, 1974 (Landrigan et al., 1976). The smelter operated during the fall and winter of 1973-74 with severely limited air pollution control capacity. Beginning in 1971, ambient concentrations of lead in the vicinity of the smelter were determined from particulate matter collected by hi-vol air samples. Data indicated that monthly average levels measured in 1974 (Figure 11-20) were three to four times the levels measured in 1971 (von Lindern and Yankel, 1976). Individual exposures of study participants to lead in the air were estimated by interpolation from these data. Air lead exposures ranged from 1.5 $\mu g/m^3$ to 30 $\mu g/m^3$ monthly average (see Figure 11-20). Soil concentrations were as high as 24,000 μg/g and averaged 7000 μg/g within one mile of the smelter. House dusts were found to contain as much as 140,000 μg/g and averaged 11,000 μg/g in homes within one mile of the complex.

The study was initiated in May, 1974 and the blood samples were collected in August, 1974 from children 1-9 years old in a door-to-door survey (greater than 90 percent participation). Social, family, and medical histories were conducted by interview. Paint, house dust, yard and garden soils, grass, and garden vegetable samples were collected. At that time, 385 of the 919 children examined (41.9 percent) had blood lead levels in excess of 40 μg/dl, 41 children (4.5 percent) had levels greater than 80 μg/dl. All but 2 of the 172 children living within 1.6 km of the smelter had levels greater than or equal to 40 μg/dl. Those two children had moved into the area less than six months earlier and had blood lead levels greater than 35 μg/dl. Both the mean blood lead concentration and the number of children classified as exhibiting excess absorption decreased with distance from the smelter (Table 11-27). Blood lead levels were consistently higher in 2- to 3-year-old children than they were in other age groups (Table 11-28). A significant negative relationship between blood lead level and hematocrit value was found. Seven of the 41 children (17 percent) with blood lead levels greater than 80 μg/dl were diagnosed as being anemic on the basis of hematocrit less than 33 percent, whereas only 16 of 1006 children (1.6 percent) with blood lead levels less than 80 μg/dl were so diagnosed. Although no overt disease was observed in children with higher lead intake, differences were found in nerve conduction velocity. Details of this finding are discussed in Chapter 12.

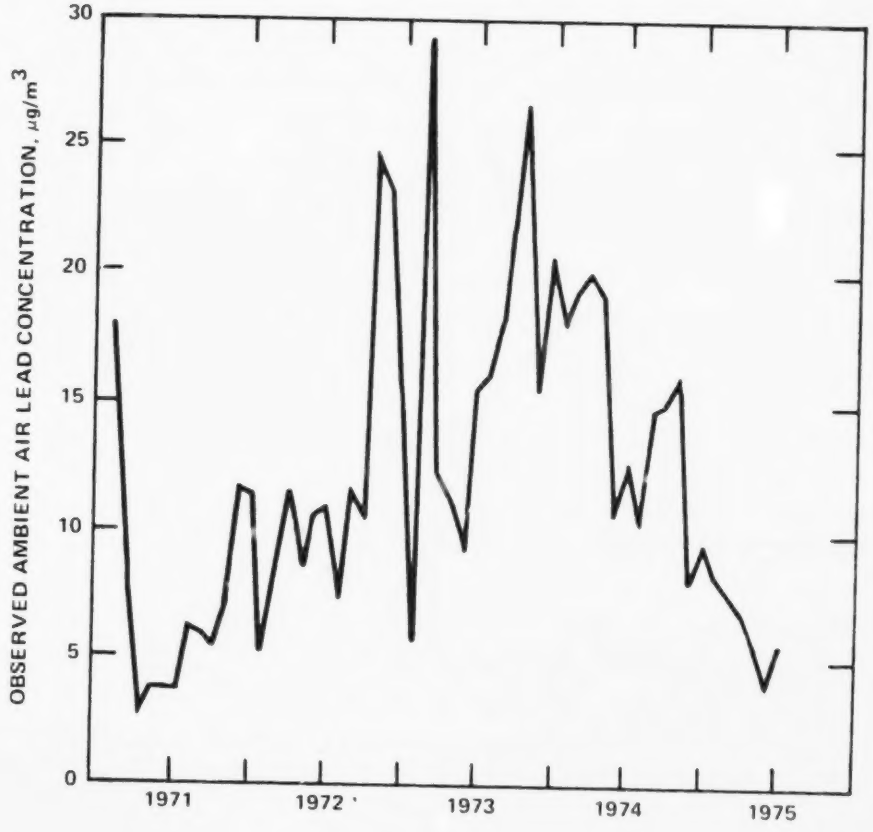


Figure 11-20. Monthly ambient air lead concentrations in Kellogg, Idaho, 1971 through 1975.

Source: von Lindern and Yankel (1976).

TABLE 11-27. GEOMETRIC MEAN BLOOD LEAD LEVELS BY AREA COMPARED WITH ESTIMATED AIR LEAD LEVELS FOR 1- TO 9-YEAR OLD CHILDREN LIVING NEAR IDAHO SMELTER. (GEOMETRIC STANDARD DEVIATIONS, SAMPLE SIZE, AND DISTANCES FROM SMELTER ARE ALSO GIVEN)[a]

Area	Geometric mean blood lead, μg/dl	GSD	Sample size	% blood lead (>40 μg/dl)	Estimated air lead, (μg/m^3)	Distance from smelter, Km
1	65.9	1.30	170	98.9	18.0	0- 1.6
2	47.7	1.32	192	72.6	14.0	1.6- 4.0
3	33.8	1.25	174	21.4	6.7	4.0-10.0
4	32.2	1.29	156	17.8	3.1	10.0-24.0
5	27.5	1.30	188	8.8	1.5	24.0-32.0
6	21.2	1.29	90	1.1	1.2	about 75

[a] EPA analysis of data from Yankel et al. (1977).

TABLE 11-28. GEOMETRIC MEAN BLOOD LEAD LEVELS BY AGE AND AREA FOR SUBJECTS LIVING NEAR THE IDAHO SMELTER (micrograms per deciliter)

Area	Age group									Teenage	Adult
	1	2	3	4	5	6	7	8	9		
1	69*	72	75	75	68	66	63	60	57	39	37
2	50	51	55	46	49	50	47	42	40	33	33
3	33	36	36	35	35	35	31	32	32	28	30
4	31	35	34	31	31	35	30	32	30		34
5	27	35	29	29	29	28	25	27	24		32
6	21	25	22	23	20	22	20	22	17		
7	28	30	28	32	30	26	37	30	20	35	32

*Error in original publication (Yankel et al., 1977).

Yankel et al. (1977) fitted the data to the following model.

$$\begin{aligned} \ln \text{(blood lead)} = 3.1 &+ 0.041 \text{ air lead} + (2.1 \times 10^{-5} \text{ soil lead}) \\ &+ 0.087 \text{ dustiness} - 0.018 \text{ age} \\ &+ 0.024 \text{ occupation} \end{aligned} \qquad (11\text{-}15)$$

where air lead was in $\mu g/m^3$; soil lead was in $\mu g/g$; dustiness was 1, 2, or 3; age was in years; and occupation (parental) was a Hollingshead index. The analysis included 879 subjects, had a multiple R^2 of 0.622, and a residual standard deviation of 0.269 (geometric standard deviation of 1.31).

Walter et al. (1980) used a similar model to examine age specific differences of the regression coefficients for the different variables. Those coefficients are summarized in Table 11-29. The variable that was most significant overall was air lead; its coefficient was approximately the same for all ages, corresponding to a change in blood lead of about 1 μg/dl per unit increase of air lead (in $\mu g/m^3$) at an air exposure of 1 $\mu g/m^3$ and about 2.4 μg/dl per unit increase in air at an air exposure of 22 $\mu g/m^3$.

TABLE 11-29. AGE-SPECIFIC REGRESSION COEFFICIENTS FOR THE ANALYSIS OF LOG (BLOOD LEAD) LEVELS IN THE IDAHO SMELTER STUDY

Age	Air	Dust	Occupation	Pica	Sex	Soil ($\times 10^4$)	Intercept	N
1	0.0467*	0.119†	0.0323	0.098	0.055	3.5	3.017	98
2	0.0405*	0.106†	0.0095	0.225*	0.002	20.6†	3.567	94
3	0.0472*	0.108†	0.0252	0.077	0.000	24.2*	3.220	115
4	0.0366*	0.107†	0.0348	0.117	0.032	32.1*	3.176	104
5	0.0388*	0.052	0.0363†	0.048	-0.081	23.4*	3.270	130
6	0.0361*	0.070	0.0369†	0.039	-0.092	38.4*	3.240	120
7	0.0413*	0.053	0.0240	0.106	-0.061	21.3†	3.329	113
8	0.0407*	0.051	0.0422†	0.010	-0.106†	16.2	3.076	105
9	0.0402*	0.081†	0.0087	0.108	-0.158*	11.6	3.477	104

* $p < 0.01$

† $p < 0.05$

The next most important variable that attained significance at a variety of ages was the household dustiness level (coded as low = 0, medium = 1, or high = 2), showing a declining effect with age and being significant for ages 1 - 4 years. This suggested age-related hygiene behavior and a picture of diminishing home orientation as the child develops. For ages 1-4 years, the coefficient indicates the child in a home with a "medium" dust level would have a blood lead level ~ 10 percent higher than a child in a home with a "low" dust level, other factors being comparable.

The coefficients for soil lead - blood lead relationships exhibited a fairly regular pattern, being highly significant ($p < 0.01$) for ages 3-6 years, and significant ($p < 0.05$) at ages 2-6 years. The maximum coefficient (at age 6) indicates a 4 percent increase in blood lead per 1000 µg/g increase in soil lead.

Pica (coded absent = 0, present = 1) had a significant effect at age 2 years, but was insignificant elsewhere; at age 2 years, an approximate 25 percent elevation in blood lead is predicted in a child with pica, compared with an otherwise equivalent child without pica.

Parental occupation was significant at ages 5, 6, and 8 years; at the other ages, however, the sign of the coefficient was always positive, consistent with a greater lead burden being introduced into the home by parents working in the smelter complex.

Finally, sex (coded male = 0; female = 1) had a significant negative coefficient for ages 8 and 9 years, indicating that boys would have lead levels 15 percent higher than girls at this age, on the average. This phenomenon is enhanced by similar, but nonsignificant, negative coefficients for ages 5-7 years.

Snee (1982c) also reanalyzed the Idaho smelter data using a log-linear model. He used dummy variables for age, work status of the father, educational level of the father, and household dust level (cleanliness). The resulting model had a multiple R^2 of 0.67 and a residual standard deviation of 0.250 (geometric standard deviation of 1.28). The model showed that 2-year-olds had the highest blood lead levels. The blood lead inhalation slope was essentially the same as that of Yankel et al. (1977) and Walter et al. (1980).

The above non-linear analyses of the Idaho smelter study are the only analyses which suggest that the blood lead to air lead slope increases with increasing air lead, contrary to the findings of decreasing slopes seen at high air lead exposures in other studies. An alternative to this would be to attempt to fit a linear model as described in Appendix 11-B. Exposure coefficients were estimated for each of the factors shown in Table 11-30. The results for the different covariates are similar to those of Snee (1982c) and Walter et al. (1980).

Because the previous analyses noted above indicated a nonlinear relationship, a similar model with a quadratic air lead term added was also fitted. The coefficients for the other factors remained about the same, and the improvement in the model was marginally significant ($p = 0.05$). This model gave a slope of 1.16 at an air lead of 1 µg/m^3, and 1.39 at an air lead of 2 µg/m^3. Both the linear and quadratic models, along with Snee's (1982b) model are shown in Figure 11-21. The points represent mean blood lead levels adjusted for the factors in Table 11-30 (except air lead) for each of the different exposure subpopulations.

TABLE 11-30. ESTIMATED COEFFICIENTS* AND STANDARD ERRORS FOR THE IDAHO SMELTER STUDY

Factor	Coefficient	Asymptotic standard error
Intercept (μg/dl)	13.19	1.90
Air lead (μg/m^3)	1.53	0.064
Soil lead (1000 μg/g)	1.10	0.14
Sex (male=1, female=0)	1.31	0.59
Pica (eaters=1, noneaters=0)	2.22	0.90
Education (graduate training=0)	-	
At least high school	3.45	1.44
No high school	4.37	1.51
Cleanliness of home (clean=0)	-	
Moderately clean	3.00	0.65
Dirty	6.04	1.06
Age (1 year old=0)	-	
2 years old	4.66	1.48
3 years old	5.48	1.32
4 years old	3.16	1.32
5 years old	2.82	1.25
6 years old	2.74	1.24
7 years old	0.81	1.23
8 years old	-0.19	1.28
9 years old	-1.50	1.21
Work status (no exposure=0)	-	
Lead or zinc worker	3.69	0.61

Residual standard deviation = 0.2576 (geometric standard deviation = 1.29).

Multiple R^2 = 0.662.

Number of observations = 860.

*Calculations made by EPA.

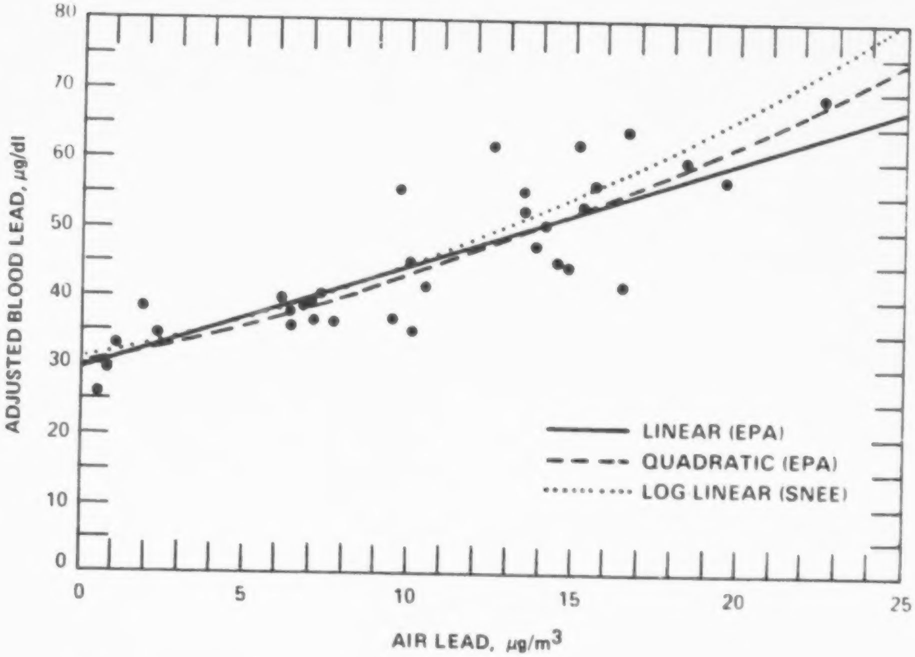


Figure 11-21. Fitted equations to Kellogg Idaho/Silver Valley adjusted blood lead data.

Yankel et al. (1977), Walter et al. (1980), and Snee (1982c) make reference to a follow-up study conducted in 1975. The second study was undertaken to determine the effectiveness of control and remedial measures instituted after the 1974 study. Between August, 1974 and August, 1975, the mean annual air lead levels decreased at all stations monitored. In order of increasing distance from the smelter, the annual mean air lead levels for the one year preceding each drawing were 18.0-10.3 μg/m^3, 14.0-8.5 μg/m^3, 6.7-4.9 μg/m^3, and 3.1-2.5 μg/m^3 at 10-24 km. Similar reductions were noted in house dust lead concentrations. In a separate report, von Lindern and Yankel (1976) described reductions in blood lead levels of children for whom determinations were made in both years. A number of factors complicate the interpretation of the followup study, including the changes in time-varying concentrations of air lead (Figure 11-20) from 1974 to 1975, and relocations of residence. The results demonstrated that significant decreases in blood lead concentration resulted from exposure reductions.

11.4.1.7 Omaha, Nebraska Studies. Exposure from both a primary and secondary smelter in the inner city area of Omaha, Nebraska, has been reported in a series of publications (Angle et al., 1974; Angle and McIntire, 1977, 1979; McIntire and Angle, 1973). During 1970-1977, children were studied from these areas: an urban school at a site immediately adjacent to a small battery plant and downwind from two other lead emission sources; from schools in a mixed commercial-residential area; and from schools in a suburban setting. Children's blood lead levels by venipuncture were obtained by macro technique for 1970 and 1971, but Delves micro assay was used for 1972 and later. The differences for the change in techniques were taken into account in the presentation of the data. Air lead values were obtained by hi-vol samplers and dustfall values were also monitored. Table 11-31 presents the authors' summary of the entire data set, showing that as air lead values decrease and then increase, dustfall and blood lead values follow. The authors used regression models, both log-linear and semilog, to calculate (air lead)/(blood lead).

Specific reports present various aspects of the work. Black children in the two elementary schools closest to the battery plant had higher blood leads (34.1 μg/dl) than those in elementary and junior high schools farther away (26.3 μg/dl). Best estimates of the air exposures were 1.65 and 1.48 μg/m^3, respectively (McIntire and Angle, 1973). The latter study compared three populations: urban versus suburban high school students, ages 14-18; urban black children, ages 10-12, versus suburban whites, ages 10-12; and blacks ages 10-12 with blood lead levels over 20 μg/dl versus schoolmates with blood lead levels below 20 μg/dl (Angle et al., 1974). The urban versus suburban high school children did not differ significantly, 22.3 ± 1.2 and 20.2 ± 7.0 μg/dl, respectively, with mean values of air lead concentrations of 0.43 and 0.29 μg/m^3. For 15 students who had environmental samples taken from their homes, correlation coefficients between blood lead levels and soil and housedust lead levels

TABLE 11-31. AIR, DUSTFALL AND BLOOD LEAD CONCENTRATIONS IN OMAHA, NE STUDY, 1970-1977[a]

Group	Air $\mu g/m^3$ (N)[b]	Dustfall, $\mu g/m^3$ - mo (N)[c]	Blood, $\mu g/dl$ (N)[d]
All urban children, mixed commercial and residential site			
1970-71	1.48 ± 0.14(7;65)	--	31.4 ± 0.7(168)
1972-73	0.43 ± 0.08(8;72)	10.6 ± 0.3(6)	23.3 ± 0.3(211)
1974-75	0.10 ± 0.03(10;72)	6.0 ± 0.1(4)	20.4 ± 0.1(284)
1976-77	0.52 ± 0.07(12;47)	8.8 (7)	22.8 ± 0.7(38)
Children at school in a commercial site			
1970-71	1.69 ± 0.11(7;67)	--	34.6 ± 1.5(21)
1972-73	0.63 ± 0.15(8;74)	25.9 ± 0.6(5)	21.9 ± 0.6(54)
1974-75	0.10 ± 0.03(10;70)	14.3 ± 4.1(4)	19.2 ± 0.9(17)
1976-77	0.60 ± 0.10(12;42)	33.9 (7)	22.8 ± 0.7(38)
All suburban children in a residential site			
1970-71	0.79 ± 0.06(7;65)	--	--
1972-73	0.29 ± 0.04(8;73)	4.6 ± 1.1(6)	19.6 ± 0.5(81)
1974-75	0.12 ± 0.05(10;73)	2.9 ± 0.9(4)	14.4 ± 0.6(31)
1976-77	--	--	18.2 ± 0.3(185)

[a] Blood lead 1970-71 is by the macro technique, corrected for an established laboratory bias of 3 μg/dl, macro-micro; all other values are by Delves micro assay.

[b] N = Number of months; number of 24-hour samples.

[c] N = Number of months.

[d] N = Number of blood samples.

Source: Adapted from Angle and McIntire, 1977.

were 0.31 and 0.29, respectively. Air, dust, and soil lead measurements at 37 sites were imputed to all children in the vicinity.

Suburban 10- to 12-year-olds had lower blood lead levels than their urban counterparts, 17.1 ± 0.7 versus 21.7 ± 0.5 μg/dl (Angle et al., 1974). Air lead exposures were higher in the urban than in the suburban population, although the average exposure remained less than 1 $\mu g/m^3$. Dustfall lead measurements, however, were very much higher; 32.96 mg/m^2/month for urban 10- to-12-year-olds versus 3.02 mg/m^2/month for suburban children.

Soil lead and house dust lead exposure levels were significantly higher for the urban black high-lead group than for the urban low-lead group. A significant correlation (r = 0.49) between blood lead and soil lead levels was found.

Angle has reanalyzed the Omaha study (Angle et al., 1984) using all of the data on children from all years. There were 1075 samples from which blood lead (μg/dl), air (μg/m³), soil (μg/g), and house dust (μg/g) lead were available. The linear regression model, fitted in logarithmic form, was

$$\underset{}{\text{Pb-Blood}} = \underset{(\pm 0.40)}{15.67} + \underset{(\pm 0.60)}{1.92}\ \text{Pb-Air} + \underset{(\pm 0.00097)}{0.00680}\ \text{Pb-Soil} + \underset{(\pm 0.00090)}{0.00718}\ \text{Pb-House Dust} \qquad (11\text{-}16)$$

$$(N = 1075,\ R^2 = 0.20,\ S^2 = 0.0901,\ GSD = 1.35)$$

Similar models fitted by age category produced much more variable results, possibly due to small ranges of variation in air lead within certain age categories.

11.4.1.8 Roels et al. Studies. Roels et al. (1976, 1978, 1980) have conducted a series of studies in the vicinity of a lead smelter in Belgium. Roels et al. (1980) report a follow-up study in 1975 that included study populations from a rural-nonindustrialized area as well as from the lead smelter area. The rural group consisted of 45 children (11-14 years). The smelter area group consisted of 69 school children from three schools. These children were divided into two groups; group A (aged 10-13) lived less than 1 km from the smelter and their schools were very close to the smelter; group B consisted of school children living more than 1.5 km from the smelter and attending a school more distant from the smelter.

In 1974 the smelter emitted 270 kg of lead and the air lead levels were 1-2 orders of magnitude greater than the current Belgian background concentration for air lead (0.23 μg/m³). Soil and vegetation were also contaminated with lead; within 1 km the soil lead level was 12,250 μg/g. The concentration of lead in drinking water was less than 5 μg/l.

Environmental assessment included air, soil, and dust. Air monitoring for lead had been continuous since September, 1973 at two sites, one for each of the two groups. In the rural area, air monitoring was done at two sites for five days using membrane pumps. Lead was analyzed by flameless atomic absorption spectrophotometry. Dust and soil samples were collected at the various school playgrounds, and were also analyzed by flameless atomic absorption. A 25 ml blood sample was collected from each child and immediately divided among three tubes. One tube was analyzed for lead content by flameless atomic absorption with background correction. Another tube was analyzed for ALA-D activity while the third was analyzed for FEP. FEP was determined by the Roels modification of the method of Sassa. ALA-D was assayed by the European standard method.

Air lead levels decreased from area A to area B. At both sites the airborne lead levels declined over the two years of monitoring. The amount of lead produced at this smelter during this time remained constant, about 100,000 metric tons/year. The median air lead level at the closer site (A) dropped from 3.2 to 1.2 μg/m^3, while at the far site (B) the median went from 1.6 to 0.5-0.8 μg/m^3. The rural area exposure levels did not vary over the study period, remaining rather constant at about 0.3 μg/m^3.

Both smelter vicinity groups showed signs of increased lead absorption relative to the rural population. Blood lead levels for group A were about three times those for the rural population (26 versus 9 μg/dl). The former blood lead levels were associated with about a 50 percent decrease in ALA-D activity and a 100 percent increase in FEP concentration. However, FEP levels were not different for group B and rural area residents.

Later surveys of children (Roels et al., 1980) were conducted in 1976, 1977, and 1978; the former two in autumn, the latter in spring. In total there were five surveys conducted yearly from 1974-1978. A group of age-matched controls from a rural area was studied each time except 1977. In 1976 and 1978 an urban group of children was also studied. The overall age for the different groups ranged from 9 to 14 years (mean 11-12). The length of residence varied from 0.5 to 14 years (mean 7-10 years). The subjects were always recruited from the same five schools: one in the urban area, one in the rural area and three in the smelter area (two <1 km and one, 2.5 km away). In all, 661 children (328 boys and 333 girls) were studied over the years. Two hundred fourteen children came from less than 1 km from the smelter, 169 children from 1.5 to 2.5 km from the plant, 55 children lived in the urban area, and 223 children lived in the rural area.

Air lead levels decreased from 1977 to 1978. However, the soil lead levels in the vicinity of the smelter were still elevated (<1 km, soil lead = 2000-6000 μg/g). Dustfall lead in the area of the near schools averaged 16.4-22.0 mg/m^2·day at 500 m from the stack, 5.8-7.2 mg/m^2·day at 700 m, about 2 mg/m^2·day at 1000 m, and fluctuated around 0.5-1 mg/m^2·day at 1.5 km and beyond. The particle size was predominantly 2 μm in diameter with a secondary peak between 4 and 9 μm. The particle size declined with increasing distance from the smelter (0.7-2.4 km).

The air lead and blood lead results for the five years are presented as Table 11-32. The reported air leads are not calendar year averages. The table shows that blood lead levels (electrothermal atomic absorption spectrophotometry) are lower in the girls than the boys. Within 1 km of the smelter no consistent improvement in air lead levels was noted over the years of the study. The mean blood leads for the children living at about 2.5 km from the smelter never exceeded 20 μg/dl since 1975, although they were higher than for urban and rural children.

TABLE 11-32. MEAN AIRBORNE AND BLOOD LEAD LEVELS RECORDED DURING FIVE DISTINCT SURVEYS (1974 to 1978) FOR STUDY POPULATIONS OF 11-YEAR-OLD CHILDREN LIVING LESS THAN 1 km OR 2.5 km FROM A LEAD SMELTER, OR LIVING IN A RURAL OR URBAN AREA

Study populations	Setting	Pb-Air, μg/m³	Blood lead concentration, μg/dl					
			Total Population		Boys		Girls	
			n	Mean ± SD	n	Mean ± SD	n	Mean ± SD
1 Survey (1974)	< 1 km	4.06	37	30.1 ± 5.7	14	31.0 ± 5.5	23	29.6 ± 5.9
	2.5 km	1.00	--	--	14	21.1 ± 3.4	--	--
	Rural	0.29	92	9.4 ± 2.1	28	9.7 ± 1.6	64	9.3 ± 2.2
2 Survey (1975)	<1 km	2.94	40	26.4 ± 7.3	19	27.4 ± 6.5	21	25.4 ± 8.1
	2.5 km	0.74	29	13.6 ± 3.3	17	14.8 ± 3.6	12	11.9 ± 1.9
	Rural	0.31	45	9.1 ± 3.1	14	8.2 ± 2.1	31	9.5 ± 3.4
3 Survey (1976)	<1 km	3.67	38	24.6 ± 8.7	18	28.7 ± 8.0	20	20.8 ± 7.6
	2.5 km	0.80	40	13.3 ± 4.4	24	15.6 ± 2.9	16	9.8 ± 3.8
	Urban	0.45	26	10.4 ± 2.0	17	10.6 ± 2.0	9	9.9 ± 2.0
	Rural	0.30	44	9.0 ± 2.0	21	9.2 ± 2.3	23	8.7 ± 1.7
4 Survey (1977)	<1 km	3.42	56	28.9 ± 6.5	27	31.7 ± 9.5	29	26.4 ± 8.7
	2.5 km	0.49	50	14.8 ± 4.7	34	15.7 ± 4.8	16	13.0 ± 4.3
5 Survey (1978)	< 1 km	2.68	43	27.8 ± 9.3	20	29.3 ± 9.8	23	26.5 ± 8.9
	2.5 km	0.54	36	16.0 ± 3.8	26	16.6 ± 3.5	10	14.3 ± 4.2
	Urban	0.56	29	12.7 ± 3.1	18	13.4 ± 2.3	11	11.5 ± 4.0
	Rural	0.37	42	10.7 ± 2.8	17	11.9 ± 3.0	25	10.0 ± 2.4

Source: Roels et al. (1980).

The researchers then investigated the importance of the various sources of lead in determining blood lead levels. Data were available from the 1976 survey on air, dust, and hand lead levels. Boys had higher hand dust lead than girls. Unfortunately, the regression analyses performed on these data were based on the group means of four groups.

EPA has reanalyzed the 1976 study using original data provided by Dr. Roels on the 148 children. The air lead, playground dust lead, and hand lead concentrations were all highly correlated with each other. The hand lead measurements are used here with due regard for their limitations, because day-to-day variations in hand lead for individual children are believed to be very large. However, even though repeated measurements were not available, this is among the most usable quantitative evidence on the role of ingested hand dust in childhood lead absorption.

Total lead content per hand is probably more directly related to ingested lead than is the lead concentration in the hand dust. The linear regression model used above was fitted by EPA using lead in air ($\mu g/m^3$), lead in hand dust (μg/hand), lead in playground dust ($\mu g/g$), and sex as covariates of blood lead. The lead variables were highly correlated, resulting in a statistically significant regression but not statistically significant coefficients. Thus the playground dust measurement was dropped and the following model obtained with almost as small a residual sum of squares,

$$\ln(\text{Pb-Blood}) = \ln(\underset{(\pm.45)^*}{7.37} + \underset{(\pm.58)^*}{2.46}\ \text{Pb-Air} + \underset{(\pm.0062)^*}{0.0195}\ \text{Pb-Hand} + \underset{(\pm0.56)^*}{2.10}\ \text{Male}) \qquad (11\text{-}17)$$

*Standard error of estimated regression coefficients.

The fitted model for the 148 observations gave an R^2 of 0.654 and a mean square error (S^2) of 0.0836 (GSD = 1.335). The significance of the estimated coefficient establishes that intake of lead-bearing dust from the hands of children does play a role in childhood lead absorption over and above the role that can be assigned to inhalation of air lead. Individual habits of mouthing probably also affect lead absorption along this pathway. Note too that the estimated inhalation slope, 2.46, is somewhat larger than most estimates for adults. However, the effect of ingestion of hand dust appears to be almost as large as the effect of air lead inhalation in children of this age (9-14 years). Roels et al. (1980), using group means, concluded that the quantitative contribution of hand lead to children's blood lead levels was far greater than that of air lead.

The high mutual correlations among air, hand, and dust lead suggest the use of their principal components or principal factors as predictors. Only the first principal component (which accounted for 91 percent of the total variance in lead exposure) proved a statistically significant covariate of blood lead. In this form the model could be expressed as:

$$\ln(\text{Pb-Blood}) = \ln(7.42 + 1.56\text{Pb-Air} + 0.0120\text{Pb-Hand} + 0.00212\text{Pb-Dust} + 2.29\ \text{Male}) \qquad (11\text{-}18)$$

The estimated standard error on the inhalation slope is ±0.47. The difference between these inhalation slope and hand lead coefficients is an example of the partial attribution of the effects of measured lead exposure sources to those sources that are not measured.

11.4.1.9 Other Studies Relating Blood Lead Levels to Air Exposure.

The present chapter has thus far evaluated the effects of atmospheric lead on blood lead in a disaggregate manner broken down according to exposure media, including direct inhalation of atmospheric lead, ingestion of particulate lead that has fallen out as dust and surface soil, and air lead ingested in consuming food and beverages (including lead absorbed from soil and added during processing and preparation). Disaggregate analyses based on various pathways for environmental lead of the type presented appear to provide a sensitive tool for predicting blood lead burdens under changes of environmental exposure. However, some authors, e.g., Brunekreef (1984) make a strong argument for the use of air lead as the single exposure criterion. Their argument is that exposure to air lead is usually of sufficient duration that the contributions along other pathways have stabilized and are proportional to the air lead concentration. In that case, the ratio between blood lead and air lead plus dust, food, and other proportional increments must be much larger than for air lead by direct inhalation alone.

The following studies provide information on the relationship of blood lead to air lead exposures using aggregate analyses that include both direct and indirect air inputs. The first group of studies are population studies which typically employed less accurate estimates of individual exposures. The second group of studies represents industrial exposures at very high air lead levels in which the response of blood lead appears to be substantially different than at ambient air levels.

The Tepper and Levin (1975) study included both air and blood lead measurements. Housewives were recruited from locations in the vicinity of air monitors. Table 11-33 presents the geometric mean air lead and adjusted geometric mean blood lead values for this study. These values were calculated by Hasselblad and Nelson (1975). Geometric mean air lead values ranged from 0.17 to 3.39 μg/m^3, and geometric mean blood lead values ranged from 12.7 to 20.1 μg/dl.

Nordman (1975) reported a population study from Finland in which data from five urban and two rural areas were compared. Air lead data were collected by stationary samplers. All levels were comparatively low, particularly in the rural environment, where a concentration of 0.025 μg/m^3 was seen. Urban-suburban levels ranged from 0.43 to 1.32 μg/m^3.

A study was undertaken by Tsuchiya et al. (1975) in Tokyo using male policemen who worked, but not necessarily lived, in the vicinity of air samplers. In this study, five zones were established based on degree of urbanization, ranging from central city to suburban. Air monitors were established at various police stations within each zone. Air sampling was conducted from September, 1971 to September, 1972; blood and urine samples were obtained from 2283 policemen in August and September, 1971. Findings are presented in Table 11-34.

Goldsmith (1974) obtained data for elementary school (9- and 10-year-olds) and high school students in 10 California communities. Lowest air lead exposures were 0.28 μg/m^3 and highest were 3.4 μg/m^3. For boys in elementary school, blood lead levels ranged from 14.3 to 23.3 μg/dl; those for girls ranged from 13.8 to 20.4 μg/dl for the same range of air lead exposures. The high school student population was made up of only males from some of the 10 towns. The air lead range was 0.77-2.75 μg/m^3, and the blood lead range was 9.0-12.1 μg/dl.

TABLE 11-33. GEOMETRIC MEAN AIR LEAD AND ADJUSTED BLOOD LEAD LEVELS FOR 11 COMMUNITIES IN STUDY OF TEPPER AND LEVIN (1975) AS REPORTED BY HASSELBLAD AND NELSON (1975)

Community	Geometric mean air lead, μg/m³	Age and smoking adjusted geometric mean blood lead, μg/dl	Sample size
Los Alamos, NM	0.17	15.1	185
Okeana, OH	0.32	16.1	156
Houston, TX	0.85	12.7	186
Port Washington, NY	1.13	15.3	196
Ardmore, PA	1.15	17.9	148
Lombard, IL	1.18	14.0	204
Washington, DC	1.19	18.7	219
Philadelphia, PA	1.67	20.1	136
Bridgeport, IL	1.76	17.6	146
Greenwich Village, NY	2.08	16.5	139
Pasadena, CA	3.39	17.6	194

Multiple $R^2 = 0.240$

Residual standard deviation = 0.262 (geometric standard deviation = 1.30)

TABLE 11-34. MEAN AIR AND BLOOD LEAD VALUES FOR FIVE ZONES IN TOKYO STUDY

Zones	Air lead μg/m³	Blood lead, μg/100 g
1	0.024	17.0
2	0.198	17.1
3	0.444	16.8
4	0.831	18.0
5	1.157	19.7

Source: Tsuchiya et al. 1975.

The high school students with the highest blood lead levels did not come from the town with the highest air lead value. However, a considerable lag time occurred between the collection and analysis of the blood samples. In one of the communities the blood samples were refrigerated rather than frozen.

Another California study (Johnson et al., 1975, 1976) examined blood lead levels in relation to exposure to automotive lead in two communities, Los Angeles and Lancaster (a city in the high desert). Los Angeles residents studied were individuals living in the vicinity of heavily traveled freeways within the city. They included groups of males and females, aged 1 through 16, 17 through 34, and 34 and over. The persons selected from Lancaster represented similar age and sex distributions. On two consecutive days, blood, urine, and fecal samples were collected. Air samples were collected from one hi-vol sampler in Los Angeles, located near a freeway, and two such samplers in Lancaster. The Los Angeles sampler collected for 7 days; the two in Lancaster operated for 14 days. Soil samples were collected in each area in the vicinity of study subjects.

Lead in ambient air along the Los Angeles freeway averaged 6.3 ± 0.7 μg/m^3 and, in the Lancaster area, the average was 0.6 ± 0.2 μg/m^3. The mean soil lead in Los Angeles was 3633 μg/g, whereas that found in Lancaster was 66.9 μg/g. Higher blood lead concentrations were found in Los Angeles residents than in individuals living in the control area for all age groups studied. Differences between Los Angeles and Lancaster groups were significant with the sole exception of the older males. Snee (1981) has pointed out a disparity between blood samples taken on consecutive days from the same child in the study. EPA reanalyses using other criteria for outlier detection and removal obtained different inhalation slopes. This calls into question the validity of using this study to quantify the air lead to blood lead relationship.

Daines et al. (1972) studied black women living near a heavily traveled highway in New Jersey. The subjects lived in houses on streets paralleling the highway at three distances: 3.7, 38.1, and 121.9 m. Air lead as well as blood lead levels were measured. Mean annual air lead concentrations were 4.60, 2.41, and 2.24 μg/m^3, respectively, for the three distances. The mean air lead concentration for the area closest to the highway was significantly different from that in both the second and third, but the mean air lead concentration of the third area was not significantly different from that of the second. The results of the blood lead determinations paralleled those of the air lead. Mean blood lead levels of the three groups of women, in order of increasing distance, were 23.1, 17.4, and 17.6 μg/dl, respectively. Again, the first group showed a significantly higher mean than the other two, but the second and third groups' blood lead levels were similar to each other. Daines et al. (1972), in the same publication, reported a second study in which the distances from the highway were 33.5

and 457 m and in which the subjects were white upper middle class women. The air lead levels were trivially different at these two distances, and the blood lead levels did not differ either. Because the residents nearest the road were already 33 m from the highway, the differences in air lead may have been insufficient to be reflected in the blood lead levels (see Chapter 7).

A summary of linear relationships for other population studies has been extracted from Snee (1981) and is shown in Table 11-35. The Fugas study is described later in Section 11.5.1.3. There is a large range of slope values (-0.1 to 3.1) with most studies in the range of 1.0-2.0. Additional information on the more directly relevant studies is given in the Summary Section 11.4.1.10.

TABLE 11-35. BLOOD LEAD-AIR LEAD SLOPES FOR SEVERAL POPULATION STUDIES AS CALCULATED BY SNEE

Study	No. subjects	Sex	Slope	95% confidence interval
Tepper & Levin (1975)	1935	Female	1.1	±1.8
Johnson et al. (1975)	65	Male	0.8	±0.7
Nordman (1975)	96	Female	0.8	±0.6
	536	Male	1.2	±1.0
Tsuchiya et al.(1975)	478	Female	0.6	±0.9
	537	Male	3.1	±2.2
Goldsmith (1974)	89	Male	-0.1	±0.7
Fugas (1977)	79	Female	0.7	±0.7
	352	Male	2.2	±0.7
Daines et al. (1972)	61	Female (spring)	1.6	±1.7
	88	Female (fall)	2.4	±1.2
Johnson et al. (1975)	37[a]	Male (children)	1.4	±0.6
	43	Female (children)	1.1	±0.6
Goldsmith (1974)	486	Male & female (children)	2.0	±1.3

[a] Outlier results for four subjects deleted.

Source: Snee, 1981.

A comprehensive review of studies of blood lead levels in children is presented by Brunekreef (1984). Many of the studies did not include covariates by which air lead slopes could be adjusted for dust or soil ingestion and other factors, leading to aggregate estimates of air lead impacts (direct and indirect) on blood lead levels. The results of some of the studies reviewed by Brunekreef are summarized in Table 11-36. Studies selected for Table 11-36 are those with identified air monitoring methods and reliable blood lead data. The range of β values that Brunekreef (1984) reports is very large, and typical values of 3-5 are larger than those adjusted slopes (1.52-2.46) derived by EPA in preceding sections. If the aggregate approach is accepted, then the blood lead versus total (both direct and indirect) air lead slope for children may be approximately double the slope (~2.0) estimated for the direct contribution due to inhaled air lead alone.

There is a great deal of information on blood lead responses to air lead exposures of workers in lead-related occupations. Almost all such exposures are at air lead levels far in excess of typical non-occupational exposures. The blood lead versus air lead slope β is very much smaller at high blood and air levels. Analyses of certain occupational exposure studies are shown in Table 11-37.

11.4.1.10 Summary of Blood Lead versus Inhaled Air Lead Relations. Any summary of the relationship of blood lead level and air lead exposure is complicated by the need for reconciling the results of experimental and observational studies. Further, defining the form of the statistical relationship is problematical due to the lack of consistency in the range and accuracy of the air lead exposure measures in the various studies.

EPA has chosen to emphasize the results of studies that relate lead in air and lead in blood under ambient conditions. At low air lead exposures there is no statistically significant difference between curvilinear and linear blood lead inhalation relationships. Colombo (1985) states that on the basis of experimental biological evidence, theory can provide a steady-state relation of blood Pb to air Pb with a curved response and that the existing PbB vs. PbA data are such that they can be fitted by several algebraically different PbA functions, including a linear relationship. Colombo concludes, however, that the linear model is preferred because it is consistent with other published models and it is much simpler in its application. Therefore EPA has fitted linear relationships (Tables 11-38, 11-39, and 11-40) to blood lead levels in the studies to be described next with the explicit understanding that the fitted relationships are intended only to describe changes in blood lead due to modest changes (of <3.0 $\mu g/m^3$) in air lead among individuals whose blood lead levels do not exceed 30 μg/dl.

The blood lead inhalation slope estimates vary appreciably from one subject to another in experimental and clinical studies, and from one study to another. The weighted slope and standard error estimates from the Griffin study in Table 11-21 (1.75 ± 0.35) were combined with

TABLE 11-36. CHARACTERISTICS OF STUDIES ON THE RELATIONSHIP BETWEEN AIR LEAD AND BLOOD LEAD IN CHILDREN

Reference	Population	Blood sampling	Quality control data	Air sampling	Unadjusted slope	Adjusted slope	Statistical model
Cavalleri et al., 1981	3-6 n=110 8-11 n=143 school populations, living close to or at >4 km from a lead smelter	venous	yes; no interlaboratory comparison	hi-vol (?)	3.3 4.0		group comparisons
Zielhuis et al., 1979 Brunekreef et al., 1981 Diemel et al., 1981	1-7 n=690 (1977) 1-3 n=95 (1978) volunteers (1976) all children in area invited (1977, 1978) participation rate >50%	venous	yes; no information about participation in interlaboratory study	hi-vol	4.0 3.6	3.6	group comparisons multiple regression, single-log (1978)
Landrigan et al., 1975 Landrigan and Baker, 1981 Morse et al., 1979	1-18 n=259 (exposed) n=499 (control) 1972 n=140 (exposed) 1977	venous	no	hi-vol	3.7 2.6		group comparison
Roels et al., 1976, 1978, 1980	10-15 n=214 exposed 10-13 n=168 intermediate 10-13 n=223 rural 10-14 n=55 urban 1974-1978 combined	venous puncture	yes; national and international interlaboratory program	low volume	4.1-7.4 2.9-5.8 8.3-31.2 5.3		group comparisons multiple regression
Yankel et al., 1977 Walter et al., 1980 Snee, 1982c	1-9 n=1149 (1974) n= 781 (1975)	venous puncture	no	hi-vol	2.4-3.3	1-1.4 1-2.5	group comparisons/ multiple regression single log
Angle et al., 1974 Angle and McIntire, 1979	1-5 urban/suburban n=242 6-18 urban/suburban/ industrial n=832 volunteers	capillary	no	hi-vol	0.66 -2.63 2.10 15.8	0.69	multiple regression, log-log covariates not included
Billick et al., 1979, 1980 Billick (1983)	0->6 n=178.533 presented for screening	venous	yes, participation CDC blood lead proficiency testing program	hi-vol		5.2 2.9	multiple regression with geometric group means as dependent variable
Brunekreef et al., 1983	4-6 n=195 nursery school populations, living in city center or in suburban area	venous	yes; international quality control program	low volume	24.5 18.5	8.5	group comparisons and multiple regression, using log/log transformations

Source: from Brunekreef (1984).

TABLE 11-37. A SELECTION OF RECENT ANALYSES ON OCCUPATIONAL 8-HOUR EXPOSURES TO HIGH AIR LEAD LEVELS

Analysis	Study	Air lead*, μg/m³	Blood lead, μg/dl	β slope
Ashford et al. (1977)	Williams et al., 1969 Globe Union Delco-Remy	50-300	40-90	0.19 0.10
King et al. (1979)	Factory 1, 1975 Factory 2a, 1975 Factory 3a, 1975	35-1200	25-90	0.032 0.07
Gartside et al. (1982)	Delco-Remy, 1974-1976	10-350	22-72	0.0514
Bishop and Hill (1983)				Nonlinear: at 50:
	Battery plants 1975-1981 A	20-170	12-50	0.081
	B	2-200	18-72	0.045
	C	7-170	22-60	0.048
	D	7-195	24-75	0.022
	E	20-140	18-60	0.045
	F	4-140	15-53	0.101

*Assumed 8-hour exposure; divide by 3 for 24-hour equivalent.

those calculated similarly for the Rabinowitz study in Table 11-24 (2.14 ± 0.47) and the Kehoe study in Table 11-25 (1.25 ± 0.35, setting subject DH = 0), yielding a pooled weighted slope estimate of 1.64 ± 0.22 μg/dl per μg/m³. There are some advantages in using these experimental studies on adult males, but certain deficiencies need to be acknowledged. The Kehoe study exposed subjects to a wide range of exposure levels while they were in the exposure chamber, but did not control air lead exposures outside the chamber. The Griffin study provided reasonable control of air lead exposure during the experiment, but difficulties in defining the non-inhalation baseline for blood lead (especially in the important experiment at 3.2 μg/m³) add much uncertainty to the estimate. The Rabinowitz study controlled well for diet and other factors and since they used stable lead isotope tracers, they had no baseline problem. However, the actual air lead exposure of these subjects outside the metabolic ward was not well determined.

Among population studies, only the Azar study provides a slope estimate in which air lead exposures are known for individuals. However, there was no control of dietary lead intake or other factors that affect blood lead levels, and slope estimates assuming only air lead and

TABLE 11-38. CROSS-SECTIONAL OBSERVATIONAL STUDY WITH MEASURED INDIVIDUAL AIR LEAD EXPOSURE

Study	Analysis	Model	R^2	Model d.f.*	Slope at an air lead of 1.0 μg/m^3	Slope at an air lead of 2.0 μg/m^3
Azar et al. (1975) Study done in 1970-1971 in five U.S. cities, total sample size = 149. Blood leads ranged from 8 to 40 μg/dl. Air leads ranged from 0.2 to 9.1 μg/m^3	Azar et al. (1975)	ln(PBB) = 0.153 ln(PBA) + separate intercepts for each group	0.502	6	2.57 (1.23, 3.91)	1.43 (0.64, 2.30)
	Snee (1982b)	ln(PBB) = 0.2669 ln(PBA + separate background for each group) + 1.0842	0.497	7	1.12 (0.29, 1.94)	0.96 (0.25, 1.66)
	Hammond et al. (1981)	$(PBB)^{-1.019}$ = 0.179 (PBA + separate background for each group)$^{0.104}$ -0.098	0.49	8	1.08	1.07
	EPA	ln(PBB) = ln(1.318 PBA + separate background for each group)	0.491	6	1.32 (0.46, 2.17)	1.32 (0.46, 2.17)
	EPA	ln(PBB) = ln(2.902 PBA - 0.257 PBA^2 + separate background for each group)	0.504	7	2.39	1.87
	EPA	ln(PBB) = ln[1.342 PBA + separate background + (age slope x age)]	0.499	7	1.34 (0.32, 2.37)	1.34 (0.32, 2.37)
	EPA	ln(PBB) = ln[1.593 PBA + common intercept + (age x separate age slope)]	0.489	7	1.59 (0.76, 2.42)	1.59 (0.76, 2.42)
	EPA	ln(PBB) = ln[1.255 PBA + separate background + (age x separate age slope)]	0.521	11	1.26 (0.46, 2.05)	1.26 (0.46, 2.05)
	EPA	ln(PBB) = 0.25 ln[PBA + separate background + (age x separate age slope)]	0.514	12	about 1.0 (varies by city)	about 1.0 (varies by city)

Note: PBB stands for blood lead (μg/dl); PBA stands for air lead (μg/m^3); slope means rate of change of blood lead per unit change in air lead at the stated air lead value. The 95 percent confidence intervals for the slope are given in parentheses. These are approximate and should be used with caution. The analyses labeled "EPA" are calculated from the original authors' data.

*d.f. = degrees of freedom.

TABLE 11-39. CROSS-SECTIONAL OBSERVATIONAL STUDIES ON CHILDREN WITH ESTIMATED AIR EXPOSURES

Study	Analysis	Model	R^2	Model d.f.*	Slope at an air lead of	
					1.0 μg/m³	5.0 μg/m³
Kellogg Idaho/Silver Valley study conducted in 1974 based on about 880 children. Air leads ranged from 0.5 to 22 μg/m³. Blood leads ranged from 11 to 164	Yankel et al. (1977)	ln(PBB) = 0.041 PBA + 2.1×10^{-5} soil + 0.087 dust - 0.018 age + 0.024 parental occupation + 3.14	0.622	6	1.16 (1.09, 1.23)	1.37 (1.27, 1.46)
	Snee (1982c)	ln(PBB) = 0.039 PBA + 0.065 ln (soil) + terms for sex, parental occupation, cleanliness, education, pica	0.666	25	1.13 (1.06, 1.20)	1.32 (1.23, 1.42)
	EPA	ln(PBB) = ln(1.53 PBA + 0.0011 soil + terms for sex, parental occupation, cleanliness, education, pica)	0.662	18	1.53 (1.40, 1.66)	1.53 (1.40, 1.66)
	EPA	ln(PBB) = ln(1.13 PBA + 0.026 PBA^2 + terms for soil, sex, parental occupation, cleanliness, education, pica)	0.656	19	1.16	1.39
	Walter et al. (1980)	ln(PBB) = separate slopes for air, dust, parental occupation, pica, sex, and soil by age	0.56 to 0.70	7	1.01 to 1.26	1.18 to 1.48
Kellogg Idaho/Silver Valley study as above restricted to 537 children with air leads below 10 μg/m³	Snee (1982a)	ln(PBB) = 0.039 PBA + 0.055 ln(soil) + terms for sex, parental occupation, cleanliness, education, pica	0.347	25	1.07 (0.89, 1.25)	1.25 (1.01, 1.50)
Roels et al. (1980)	Roels et al. (1980) based on 8 groups	PBB = 0.007 PBA + 11.50 log(Pb-Hand) - 4.27	0.65	3	0.007	0.007
	EPA analysis on 148 subjects	ln(PBB) = ln(2.46 PBA + 0.0195 (Pb-Hand) + 2.1 (Male) + 7.37)	0.654	4	2.46 (1.31, 3.61)	2.46 (1.31, 3.61)
Angle and McIntire (1979)	Angle and McIntire (1979) on 832 samples ages 6-18	ln(PBB) = ln(8.1) + 0.03 ln(PBA) + 0.10 ln(Pb-Soil) + 0.07 ln(Pb-House Dust)	0.21	4	0.6	0.14
	832 samples ages 6 to 18	ln(PBB) = ln (4.40 PBA + 0.00457 Pb-Soil + 0.00336 Pb-House Dust + 16.21)	0.262	4	4.40 (3.20, 5.60)	4.40 (3.20, 5.60)
	Angle et al. (1984) on 1074 samples for ages 1-18	ln(PBB) = ln(1.92 PBA + 0.00680 Pb-Soil + 0.00718 Pb-House Dust + 15.67)	0.199	4	1.92 (0.74, 3.10)	1.92 (0.74, 3.10)

Note: PBB stands for blood lead (μg/dl); PBA stands for air lead (μg/m³); slope means rate of change of blood lead per unit change in air lead at the stated air lead value. The 95 percent confidence intervals for the slope are given in parentheses. These are approximate and should be used with caution. The analyses labeled "EPA" are calculated from the original authors' data.

*d.f.= degrees of freedom.

TABLE 11-40. LONGITUDINAL EXPERIMENTAL STUDIES WITH MEASURED INDIVIDUAL AIR LEAD EXPOSURE

Experiment	Analysis	Model	Air lead, $\mu g/m^3$	Blood lead, $\mu g/dl$
Kehoe 1950-1971 1960-1969	Gross (1981)	Δ PBB = 0.57 Δ PBA		
	Hammond et al.(1981)	Δ PBB = $\beta_i \Delta$ PBA, β_i by subject from -0.6 to 2.94	0.6 to 36	18 to 41
	Snee (1981)	Δ PBB = $\beta_i \Delta$ PBA, β_i by subject from 0.4 to 2.4	0.6 to 36	18 to 41
	EPA	PBB = β_i PBA + background, β_i by subject from -.34 to 2.60	0.6 to 36	18 to 41
			0.6 to 9	18 to 29
Griffin et al. 1971-1972	Knelson et al.(1973)	Δ PBB = 0.327 PBA + 3.236 + (2.10 PBA + 1.96) (ln PBA + β_i) by subject	0.15, 3.2	11 to 32
	Hammond et al.(1981)	Δ PBB = β Δ PBA, β = 1.90 at 3.2 and β = 1.54 at 10.9	0.15, 10.9	14 to 43
	Snee (1981)	Δ PBB = β_i Δ PBA, β_i by subject, β = 2.3 at 3.2 and β = 1.5 at 10.9		
	EPA	Δ PBB = β_i Δ PBA, β_i by subject, mean β = 1.52 at 3.2 and β = 1.77 at 10.9		
Chamberlain et al. 1973-1978	Chamberlain et al. (1978)	Δ PBB = β ΔPBA, β = 1.2 calculated		
	EPA	Δ PBB = β ΔPBA, β = 2.7 calculated		
Rabinowitz et al. 1973-1974	Snee (1981)	Δ PBB = β_i ΔPBA, β_i by subject from 1.7 to 3.9	0.2 to 2	14 to 28
	EPA	Δ PBB = β_i ΔPBA, β_i by subject from 1.59 to 3.56		

location as covariables (1.32 ± 0.38) are not significantly different from the pooled experimental studies.

Snee and Pfeifer (1983) have extensively analyzed the observational studies, tested the equivalence of slope estimates using pooled within-study and between-study variance components, and estimated the common slope. The result of five population studies on adult males (Azar, Johnson, Nordman, Tsuchiya, Fugas) was an inhalation slope estimate ±95 percent confidence limits of 1.4 ± 0.6. For six populations of adult females [Tepper-Levin, Johnson, Nordman, Goldsmith, Daines (spring), Daines (fall)], the slope was 0.9 ± 0.4. For four populations of children [Johnson (male), Johnson (female), Yankel, Goldsmith], the slope estimate was 1.3 ± 0.4. The between-study variance component was not significant for any group so defined, and when these groups were pooled and combined with the Griffin subjects, the slope estimate for all subjects was 1.2 ± 0.2.

The Azar slope estimate was not combined with the experimental estimates because of the lack of control on non-inhalation exposures. Similarly, the other population studies in Table 11-35 were not pooled because of the uncertainty about both inhalation and non-inhalation lead exposures. These studies, as a group, have lower slope estimates than the individual experimental studies.

There are no experimental inhalation studies on adult females or on children. The inhalation slope for women should be roughly the same as that for men, assuming proportionally smaller air intake and blood volume. The assumption of proportional size is less plausible for children. Slope estimates for children from population studies have been used in which some other important covariates of lead absorption were controlled or measured, e.g., age, sex, and dust exposure in the environment or on the hands. Inhalation slopes were estimated for the studies of Angle and McIntire (1.92 ± 0.60), Roels (2.46 ± 0.58), and Yankel et al. (1.53 ± 0.064). The standard error of the Yankel study is extremely low and a weighted pooled slope estimate for children would reflect essentially that study alone. In this case the small standard error estimate is attributable to the very large range of air lead exposures of children in the Silver Valley (up to 22 $\mu g/m^3$). The relationship is in fact not linear, but increases more rapidly in the upper range of air lead exposures. The slope estimate at lower air lead concentrations may not wholly reflect uncertainty about the shape of the curve at higher concentrations. The median slope of the three studies is 1.92.

This estimate was not combined with the child population studies of Johnson or Goldsmith. The Johnson study slope estimate used air lead measured at only two sites and is sensitive to assumptions about data outliers (Snee, 1981), which adds a large non-statistical uncertainty to the slope estimate. The Goldsmith slope estimate for children (2.0 ± 0.65) is close to the estimate derived above, but was not used due to non-statistical uncertainties about blood lead collection and storage.

One can summarize the situation briefly:

(1) The experimental studies at lower air lead levels, 3.2 μg/m³ or less, and lower blood levels, typically 30 μg/dl or less, have linear blood lead inhalation relationships with slopes β_i of 0-3.6 for most subjects. A typical value of 1.64 ± 0.22 may be assumed for adults.

(2) Population cross-sectional studies at lower air lead and blood lead levels are approximately linear with slopes β of 0.8-2.0 for inhalation contributions.

(3) Cross-sectional studies in occupational exposures in which air lead levels are higher (much above 10 μg/m³) and blood lead levels are higher (above 40 μg/dl), show a much more shallow linear blood lead inhalation relation. The slope β is in the range 0.03-0.2.

(4) Cross-sectional and experimental studies at levels of air lead somewhat above the higher ambient exposures (9-36 μg/m³) and blood leads of 30-40 μg/dl can be described either by a nonlinear relationship with decreasing slope or by a linear relationship with intermediate slope, approximately β = 0.5. Several biological mechanisms for these differences have been discussed (Hammond et al., 1981; O'Flaherty et al., 1982; Chamberlain, 1983; Chamberlain and Heard, 1981). Since no explanation for the decrease in steepness of the blood lead inhalation response to higher air lead levels has been generally accepted at this time, there is little basis on which to select an interpolation formula from low air lead to high air lead exposures. The increased steepness of the inhalation curve for the Silver Valley/ Kellogg study is inconsistent with the other studies presented. It may be that smelter situations are unique and must be analyzed differently, or it may be that the curvature is the result of imprecise exposure estimates.

(5) The blood lead inhalation slope for children is at least as steep as that for adults, with a median estimate of 1.92 from three major studies (Yankel et al., 1977; Roels et al., 1980; Angle and McIntire, 1979).

(6) Slopes which include both direct (inhalation) and indirect (via soil, dust, etc.) air lead contributions are necessarily higher than those estimates for inhaled air lead alone. Studies using aggregate analyses (direct and indirect air impacts) typically yield slope values in the range 3-5, about double the slope due to inhaled air lead alone.

11.4.2 Dietary Lead Exposures Including Water

Another major pathway by which lead enters the body is by ingestion. As noted in Chapters 6 and 7, the recycling of both natural and anthropogenic lead in the environment results in a certain amount of lead being found in the food we eat and the water we drink. Both of these environmental media provide external exposures to lead that ultimately increase internal exposure levels in addition to internal lead elevations caused by direct inhalation of lead in air. The Nutrition Foundation (1982) report presents a compilation of recent estimates of dietary intakes in the United States and Canada. The report gives information on relationships between external lead exposures and blood lead levels. The mechanisms and absorption rates for uptake of lead from food and water are described in Chapter 10. The purpose of the present section is to establish (analogously to Section 11.4.1) the relationships between external exposures to lead in food and drinking water and resulting internal lead exposures.

The establishment of these external and internal lead exposure relationships for the environmental media of food and water, however, is complicated by the inherent relationship between food and water. First, the largest component of food by weight is water. Second, drinking water is used for food preparation and, as shown in Section 7.3.1.3, provides additional quantities of lead that are appropriately included as part of external lead exposures ascribed to food. Third, the quantity of liquid consumed daily by people varies greatly and substitutions are made among different sources of liquid: soft drinks, coffee, tea, etc., and drinking water. Therefore, at best, any values of water lead intake used in drinking water calculations are somewhat problematic.

A further troubling fact is the influence of lead in the construction of plumbing facilities. Studies discussed in Section 7.3.2.1.3 have pointed out the substantial lead exposures in drinking water that can result from the use of lead pipes in the delivery of water to the tap. This problem is thought to occur only in limited geographic areas in the United States. However, where the problem is present, substantial water lead exposures occur. In these areas one cannot make a simplifying assumption that the lead concentration in the water component of food is similar to that of drinking water; rather, one is adding a potentially major additional lead exposure to the equation.

Studies that have attempted to relate blood lead levels to ingested lead exposure have used three approaches to estimate the external lead exposures involved: duplicate meals, fecal lead determinations, and market basket surveys. In duplicate diet studies, estimated lead exposures are assessed by having subjects put aside a duplicate of what they eat at each meal for a limited period of time. These studies probably provide a good, but short term, estimate of the ingestion intake. However, the procedures available to analyze lead in foods have historically been subject to inaccuracies. Hence, the total validity of data from this approach has not been established. Studies relying on the use of fecal lead determinations face two major difficulties. First, this procedure involves the use of a mathematical estimate of the overall absorption coefficient from the gut to estimate the external exposure. Until recently, these estimates have not been well documented and were assumed to be relatively constant. Newer data discussed later show a much wider variability in the observed absorption coefficients than was thought to be true. These new observations cloud the utility of studies using this method to establish external/internal exposure relationships. Secondly, it is difficult to collect a representative sample.

The last approach is the market basket approach. This approach uses the observed lead concentrations for a variety of food items coupled with estimated dietary consumption of the particular food items. Some studies use national estimates of typical consumption patterns upon which to base the estimated exposures. Other studies actually record the daily dietary intakes. This approach faces similar analytic problems to those found in the duplicate diet approach. It also faces the problem of getting accurate estimates of dietary intakes. The most current total diet study (Pennington, 1983) is described in Section 7.3.1.2.

Exposures to lead in the diet are thought to have decreased since the 1940's. Estimates from that period were in the range of 400-500 μg/day for U.S. populations. Khandekar et al. (1984) report a dietary intake of lead to be 245 μg/day. This was calculated from the lead content in different food groups and the amount of each food group consumed by an average resident of Bombay, India. Current estimates for U.S. populations are under 100 μg/day for adults. Unfortunately, a good historical record regarding the time course of dietary exposures is not available. In the years 1978-1982, efforts have been made by the American food canning industry in cooperation with the FDA to reduce the lead contamination of canned food. Data presented in Section 7.3.1.2.5 confirm the success of this effort. Seasonal variations in blood lead might also be partially attributable to seasonal variations in the dietary intake of lead. The following evidence suggests that this does not happen. Table 11-41 is taken from Human Nutrition Information Service (1983). The data suggest the following pattern: (1) Consumption of canned vegetables and fruits is much lower in the spring and summer, much higher in the fall and winter, which is the opposite of the pattern of blood lead level variations and suggests that the attribution of seasonal changes to gasoline lead may be an underestimate of its effects. (2) The pattern is similar for central city, suburban, and nonmetropolitan households. (3) There is little seasonal variation for fruit and vegetable juices and milk, and a slight increase of soft drink consumption in the summer. The magnitude of such variations is too small to account for blood lead.

The specific studies available for review regarding dietary exposures will be organized into three major divisions: lead ingestion from typical diets, lead ingestion from experimental dietary supplements, and inadvertent lead ingestion from lead plumbing.

11.4.2.1 Lead Ingestion from Typical Diets.

11.4.2.1.1 Ryu study on infants and toddlers. Ryu et al. (1983) reported a study of four breast-fed infants and 25 formula-fed infants from 8-196 days of age. At 112 days of the study, the formula-fed infants were separated into subgroups based upon how they were to receive their milk: homogenized whole cow milk obtained in cartons from a local dairy, a commercially available milk-based formula supplied in quart cans, and homogenized whole cow milk

TABLE 11-41. HOUSEHOLD CONSUMPTION OF CANNED FOODS
(pounds per week)

Food	Spring	Summer	Fall	Winter
Canned fruits*				
Central city	0.65	0.47	0.59	0.74
Suburban	0.85	0.55	0.84	0.91
Nonmetropolitan	0.83	0.62	0.78	0.85
Canned vegetables*				
Central city	2.37	2.36	2.81	2.83
Suburban	2.40	2.08	2.57	2.86
Nonmetropolitan	2.37	1.94	2.46	2.89
Fresh fluid milk				
Central city	13.44	14.20	14.31	13.75
Suburban	17.66	17.12	17.38	17.17
Nonmetropolitan	15.11	16.17	16.16	16.70
Processed milk				
Central city	1.14	1.12	1.18	1.30
Suburban	1.43	1.13	1.10	1.14
Nonmetropolitan	1.56	1.36	1.59	1.90
Canned veg. juices*				
Central city	0.39	0.38	0.37	0.35
Suburban	0.42	0.41	0.54	0.47
Nonmetropolitan	0.56	0.38	0.46	0.53
Canned fruit juices*				
Central city	1.34	1.46	1.39	1.41
Suburban	1.16	1.26	1.25	1.24
Nonmetropolitan	1.29	1.22	1.49	1.35
Soft drinks (total)				
Central city	5.50	5.75	5.11	5.3[illegible]
Suburban	6.53	6.88	6.22	5.96
Nonmetropolitan	5.67	5.89	5.62	5.25

*Commercially canned.

supplied in quart cans and heat-treated in the same manner as the commercially available formula. There were 10, 4, and 3 infants in each of these groups, respectively. In addition to food concentrations, data were collected on air, dust, and water lead. Hemoglobin and FEP were also measured.

The trends in blood lead for the formula-fed infants are shown in Table 11-42. The results up to day 112 are averaged for all 25 infants. The estimated average intake was 17 µg/day for this time period. After day 112, the subgroup of seven infants fed either canned formula or heat-treated cow's milk in cans (higher lead), had average estimated lead intake of 61 µg/day. This resulted in an increase of 7.2 µg/dl in the average blood lead level in response to an increase of 45 µg/day in lead intake by day 196. However, since the blood lead levels in this group had not reached equilibirum by this point, the slope calculated from this data of 0.16 should be regarded as an underestimate.

TABLE 11-42. BLOOD LEAD LEVELS AND LEAD INTAKE VALUES FOR INFANTS IN THE STUDY OF RYU ET AL.

Age, days	Blood lead of combined group, µg/dl		Average lead intake of combined group, µg/day	
8	8.9		17	
28	5.8		17	
56	5.1		17	
84	5.4		17	
112	6.1		17	
	Lower lead	Higher lead	Lower lead	Higher lead
140	6.2	9.3	16	61
168	7.0	12.1	16	61
196	7.2	14.4	16	61

Source: Ryu et al. (1983).

11.4.2.1.2 Rabinowitz infant study. As part of a longitudinal study of the sources of current urban lead exposure, lead was measured in 100 breast milk samples and in 73 samples of the infant formula used by non-nursing mothers (Rabinowitz et al., 1985a). Also, the blood lead levels of the infants fed these diets were determined at birth and at six months of age. Among the infants who were breast-fed, the lead content of their milks correlated very well with their six-month blood lead levels ($r = 0.42$, $p = 0.0003$). The mean lead content of infant formulas and breast milk were not significantly different, nor was the blood lead of children fed one or the other. Lead levels in maternal milk correlated poorly with umbilical cord blood lead ($r = 0.18$, $p = 0.10$). Since milk represents much of the diet of young infants and because breast milk lead levels are stable, it is possible to relate blood lead and daily dosage in this population.

11.4.2.1.3 Rabinowitz adult study. This study on male adults was described in Section 11.4.1 and in Chapter 10, where ingestion experiments were analyzed in more detail (Rabinowitz et al., 1980). As in other studies, the fraction of ingested stable isotope lead tracers absorbed into the blood was much lower when lead was consumed with meals (10.3 ± 2.2 percent) than between meals (35 ± 13 percent). Lead nitrate, lead sulfide, and lead cysteine as carriers made little difference. The much higher absorption of lead on an empty stomach implies greater significance of lead ingestion from leaded paint and from dust and soil when consumed between meals, as seems likely to be true for children.

11.4.2.1.4 Hubermont study. Hubermont et al. (1978) conducted a study of pregnant women living in rural Belgium because their drinking water was suspected of being lead-contaminated. This area was known to be relatively free of air pollution. Seventy pregnant women were recruited and asked to complete a questionnaire. Information was obtained on lifetime residence history, occupational history, smoking, and drinking habits. First flush tap water samples were collected from each home with the water lead level determined by flameless atomic absorption spectrophotometry. Biological samples for lead determination were taken at delivery. A venipuncture blood sample was collected from the mother, as was a fragment of the placenta; an umbilical cord blood sample was used to estimate the newborn's blood lead status.

For the entire population, first-flush tap water samples ranged from 0.2 to 1228.5 μg/l. The mean was 109.4, while the median was 23.2. The influence of water lead on the blood lead of the mother and infants was examined by categorizing the subjects on the basis of the lead level of the water sample, below or above 50 μg/l. Table 11-43 presents the results of this study. A significant difference in blood lead levels of mothers and newborns was found for the water lead categories. Placenta lead levels also differed significantly between water lead groups. The fitted regression equation of blood lead level for mothers is given in summary Table 11-51 in section 11.4.2.4.

11.4.2.1.5 Sherlock studies. Sherlock et al. (1982) reported a study from Ayr, Scotland, which considered both dietary and drinking water lead exposures for mothers and children living in the area. In December, 1980, water lead concentrations were determined from kettle water from 114 dwellings in which the mother and child lived less than five years. The adult women had venous blood samples taken in early 1981 as part of a European Economic Community (EEC) survey on blood lead levels. A duplicate diet survey was conducted on a random sample of these 114 women stratified by kettle water lead levels.

A study population of 11 mothers with infants less than 4 months of age agreed to participate in the infant survey. A stratified sample of 31 of 47 adult volunteers was selected to participate in the duplicate diet study.

Venous blood samples for adults were analyzed for lead immediately before the duplicate diet study; in some instances additional samples were taken to give estimates of long-term

TABLE 11-43. INFLUENCE OF LEVEL OF LEAD IN WATER ON BLOOD LEAD LEVEL IN BLOOD AND PLACENTA

Comparison group	Water level	Mean	Median	Range	Significance
Age (years)	Low**	25.6	24	18-41	NS*
	High***	26.3	25	20-42	
Pb-B mother (μg/dl)	Low	10.6	9.9	5.1-21.6	<0.005
	High	13.8	13.1	5.3-26.3	
Pb-B newborn (μg/dl)	Low	8.8	8.5	3.4-24.9	<0.001
	High	12.1	11.9	2.9-22.1	
Pb placenta (μg/100 g)	Low	9.7	8.2	4.4-26.9	<0.005
	High	13.3	12.0	7.1-28	
Water Pb (μg/l)	Low	11.8	6.3	0.2-43.4	
	High	247.4	176.8	61.5-1228.5	

Source: Hubermont et al. (1978)

*NS means not significant.

**Water lead <50 μg/l.

***Water lead >50 μg/l.

exposure. Venous samples were taken from the infants immediately after the duplicate diet week. Blood lead levels were determined by AAS with a graphite furnace under good quality control. Two other laboratories analyzed each sample by different methods. The data reported are based on the average value of the three methods.

Dietary intakes for adults and children were quite different; adults had higher intakes than children. Almost one-third of the adults had intakes greater than 3 mg/week while only 20 percent of the infants had that level of intake. Maximum values were 11 mg/week for adults and 6 mg/week for infants. The observed blood lead values in the dietary study had the distributions shown in Table 11-44.

Table 11-45 presents the crosstabulation of drinking water lead and blood lead level for the 114 adult women in the study. A strong trend of increasing blood lead levels with increasing drinking water lead levels is apparent. A curvilinear regression function fits the data better than a linear one. A similar model including weekly dietary intake was fitted to the data for adults and infants. These models are in summary Tables 11-49 and 11-52 in Section 11.4.2.4.

TABLE 11-44. DISTRIBUTIONS OF OBSERVED BLOOD LEAD VALUES IN AYR

Groups	Blood lead values		
	>20 µg/dl	>30 µg/dl	>35 µg/dl
Adults	55%	16%	2%
Infants	100%	55%	36%
EEC directive	50%	10%	2%

TABLE 11-45. BLOOD LEAD AND KETTLE WATER LEAD CONCENTRATIONS FOR ADULT WOMEN LIVING IN AYR

Blood lead, µg per 100 ml	Water lead, µg/l							
	<10	11-99	100-299	300-499	500-999	1000-1499	>1500	Total
<10	8	5						13
11-15	4	7	3	2			1	17
16-20	1	3	12	3	3			22
21-25		4	9	7	5			25
26-30			2	4	4	2		12
31-35			2	1	2	2	3	10
36-40				1	1	1	1	4
>40				1	4	3	3	11
Total	13	19	28	19	19	8	8	114

The researchers also developed a linear model for the relationship between dietary intake and drinking water lead. The equation indicates that, when the concentration of lead in water was about 100 µg/l, approximately equal amounts of lead would be contributed to the total week's intake from water and diet; as water lead concentrations increase from this value, the principal contributor would be water.

A follow-up study on this same population was made from December, 1982 to March, 1983, as reported by Sherlock et al. (1984). In April 1981, the pH of the water supply was increased from pH 4.5-5.5 to about pH 8.5 by the addition of lime. The result was a decrease in the median blood lead level from 21 to 13 µg/dl. The combined data set was used to give the regression equation shown in Table 11-52 in Section 11.4.2.4.

11.4.2.1.6 Central Directorate on Environmental Pollution study. The United Kingdom Central Directorate on Environmental Pollution (1982) studied the relationship between blood lead level and dietary and drinking water lead in infants. Subjects were first recruited by soliciting participation of all pregnant women attending two hospitals and residing within a single water distribution system. Each woman gave a blood sample and a kettle water sample. The women were then allocated to one of six potential study groups based on the concentration of water lead.

At the start of the second phase (duplicate diet) a total of 155 women volunteered (roughly 17-32 per water lead level category). During the course of the study, 24 mothers withdrew; thus a final study population of 131 mothers was achieved.

When the children reached 13 weeks of age, duplicate diet for a week's duration was obtained for each infant. Great care was exerted to allow collection of the most accurate sample possible. Also, at this time a variety of water samples were collected for subsequent lead analysis.

Blood samples were collected by venipuncture from mothers before birth, at delivery, and about the time of the duplicate diet. A specimen was also collected by venipuncture from the infant at the time of the duplicate diet. The blood samples were analyzed for lead by graphite furnace AAS with deuterium background correction. Breast milk was analyzed analogously to the blood sample after pretreatment for the different matrix. Water samples were analyzed by flame atomic absorption; food samples were analyzed after ashing by flameless atomic absorption.

Both mothers and infants exhibited increased lead absorption by EEC (European Economic Community) directive standards. The infants generally had higher blood leads than the mothers. However, in neither population was there evidence of substantial lead absorption.

Water lead samples ranged from less than 50 to greater than 500 µg/l, which was expected due to the sampling procedure used. First draw samples tended to be higher than the other samples. The composite kettle samples and the random daytime samples taken during the duplicate diet week were reasonably similar: 59 percent of the composite kettle samples contained up to 150 µg/l, as did 66 percent of the random daytime samples.

Lead intakes from breast milk were lower than from duplicate diets. The lead intakes estimated by duplicate diet analysis ranged from 0.04 to 3.4 mg/week; about 1/4 of the diets had intakes less than 1.0 mg/week. The minimum intakes were truncated, as the limit of detection for lead was 10 µg/kg and the most common diets weighed 4 kg or more.

The central directorate data were reanalyzed by Lacey et al. (1985). Results from both Lacey et al. (1985) and the United Kingdom Central Directorate on Environmental Pollution (1982) are in Tables 11-49 to 11-52 in section 11.4.2.4. The authors used both linear and cube root models to describe their data. Models relating blood lead levels of infants to dietary intake are in Table 11-49 in Section 11.4.2.4. Models relating blood lead levels for both mothers and infants to first flush water lead levels and running water lead levels are in Tables 11-51 and 11-52 in Section 11.4.2.4 respectively. In most cases, the nonlinear (cubic) model provided the best fit. Figure 11-22 illustrates the fit for the two models showing infant blood lead levels versus dietary lead intake.

11.4.2.1.7 Pocock study. Pocock et al. (1983) have recently reported an important study examining the relationship in middle-aged men of blood lead level and water lead levels. Men aged 40-59 were randomly selected from the registers of general practices located in 24 British towns. Data were obtained between January, 1978 and June, 1980.

Blood lead levels were obtained on 95 percent of the 7378 men originally selected. The levels were determined by microatomic absorption spectrophotometry. A strict internal and external quality control program was maintained on the blood lead determinations for the entire study period. Tap water samples were obtained on a small subset of the population. About 40 men were chosen in each of the 24 towns to participate in the water study. First draw samples were collected by the subjects themselves, while a grab daytime and flushed sample were collected by study personnel. These samples were analyzed by several methods of AAS depending on the concentration range of the samples.

Blood lead and water lead levels were available for a total of 910 men from 24 towns. Table 11-46 displays the association between blood lead levels and water lead levels. Blood lead levels nearly doubled from the lowest to highest water lead category.

The investigators analyzed their data further by examining the form of the relationship between blood and water lead. This was done by categorizing the water lead levels into nine intervals of first draw levels. The first group (<6 μg/l) had 473 men while the remaining eight intervals had ~ 50 men each. Figure 11-23 presents the results of this analysis. The authors state, "The impression is that mean blood lead increases linearly with first draw water lead except for the last group with very high water concentrations." The regression line shown in the figure is only for men with water lead levels less than 100 μg/l, and is given in Table 11-51 in Section 11.4.2.4. A separate regression was done for the 49 men whose water lead exposures were greater than 100 μg/l. The slope for the second line was only 23 percent of the first line.

Additional analyses were done examining the possible influence of water hardness on blood lead levels. A strong negative relationship (r = 0.67) was found between blood lead level and water hardness. There is a possibility that the relationship between blood lead and water hardness was due to the relationship of water hardness and water lead. It was found that a relationship with blood lead and water hardness still existed after controlling for water lead level.

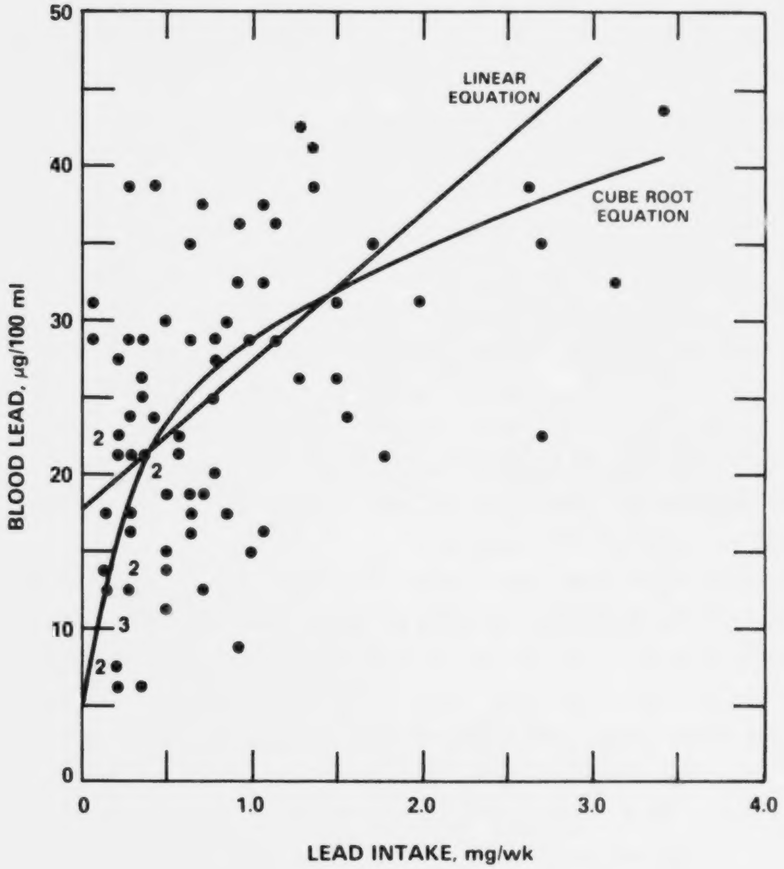


Figure 11-22. Blood lead concentrations versus weekly lead intake for bottle-fed infants. (Numbers are coincidental points.)

Source: United Kingdom Central Directorate on Environmental Pollution (1982).

TABLE 11-46. RELATIONSHIP OF BLOOD LEAD
AND WATER LEAD IN 910 MEN AGED 40-59 FROM 24 BRITISH TOWNS

First draw water lead, μg/l	Number of men	Mean blood lead (μg/dl)	Standard deviation	% with blood lead >35 μg/dl
<50	789	15.06	5.53	0.7
50-99	69	18.90	7.31	4.3
100-299	40	21.65	7.83	7.5
≧300	12	34.19	15.27	41.7
Total	910	15.89	6.57	1.9
Daytime water lead, μg/l				
<50	845	15.31	5.64	0.7
50-99	36	19.62	7.89	8.3
100-299	23	24.78	9.68	17.4
≧300	5	39.78	15.87	60.0
Total	909	15.85	6.44	1.8

Source: Pocock et al. (1983).

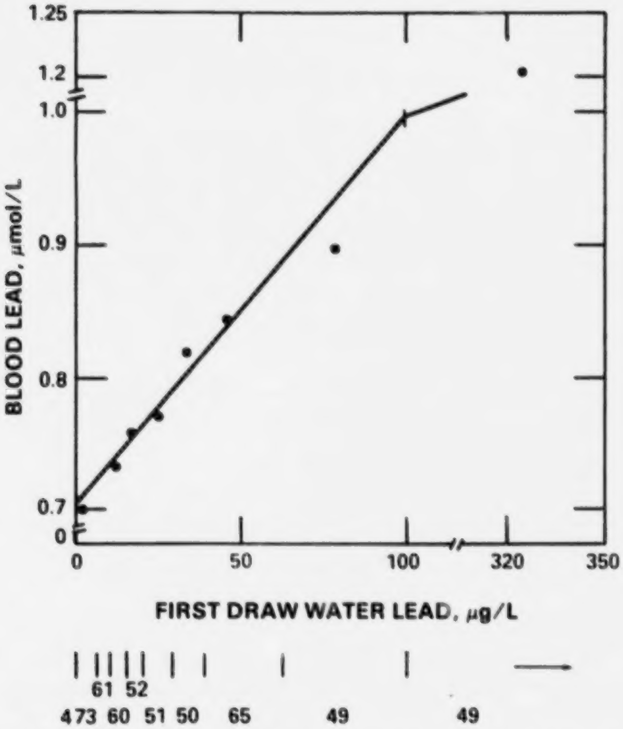


Figure 11-23. Mean blood lead for men grouped by first draw water concentration.

Source: Pocock et al. (1983).

The authors come to the following conclusion regarding the slope of the relationship between blood lead and water lead:

> This study confirms that the relation is not linear at higher levels. Previous research had suggested a power function relationship--for example, blood lead increases as the cube root of water lead. Our data, based on a large and more representative sample of men, do not agree with such a curve, particularly at low concentrations of water lead.

11.4.2.1.8 Thomas study. Thomas et al. (1981) studied blood lead levels among residents of a hardwater area in the United Kingdom. They recruited a random sample of voters in an area with 320 ppm calcium hardness. A tap water sample using first draw water was requested and was returned by 70 percent of the selected voters. Sixty women in the dwellings with the highest water blood level and 30 randomly selected women in dwellings in the lowest water lead levels were selected for a blood lead determination; 84 women responded. Blood lead levels were stratified by water lead levels and were compared to data gathered elsewhere from softwater areas. Substantial differences were noted, with the residents of the hardwater areas having meaningfully lower blood lead levels. This is true even for residents in the hardwater area with the lowest (<0.05 mg/l) water lead level.

11.4.2.1.9 Elwood study. Elwood et al. (1983) have investigated the potential of the degree of water hardness to influence the relationship between lead concentrations in drinking water and blood lead level. An experimental model was employed wherein two groups of women were studied both before and after the water hardness of the drinking water for one group was changed to 100 from 10 mg/l. Postconversion blood lead levels were obtained 6 months later.

Mean water lead levels fell slightly after the change in the area where the water was hardened, whereas it increased slightly in the central area. Blood lead levels decreased in the experimental areas while increasing in the central area. The decline in blood lead levels was greater with increasing initial water lead levels.

11.4.2.2. Lead Ingestion from Experimental Dietary Supplements.

11.4.2.2.1 Kehoe study. Experimental studies have been used to study the relationship of food lead and blood lead levels. Gross (1981) reanalyzed the results of Kehoe. Oral doses of lead included 300, 1000, 2000, and 3000 µg/day. Each subject had a control period and an exposure period. Some also had a post-exposure period. Blood samples were collected by venipuncture and analyzed by spectrographic and dithizone methods during the study years. The ingestion doses were in addition to the regular ingestion of lead from the diet. The results of the dose response analysis for blood lead concentrations are summarized in Table 11-47.

TABLE 11-47. DOSE-RESPONSE ANALYSIS FOR BLOOD LEAD LEVELS IN THE KEHOE STUDY AS ANALYZED BY GROSS (1981)

		Difference from control[1]			
Subject	Added lead, μg/day	Diet, μg/day	Feces, μg/day	Urine, μg/day	Blood, μg/dl
SW	300	308	208	3	-1
MR	1000	1072	984	55	17
EB	2000	1848	1547	80	33
IF[2]	3000	2981	2581	49	19

[1] Each subject servced as his own control.

[2] Subject did not reach equilibrium.

Both subjects MR and EB had long exposure periods, during which time their blood lead levels increased to equilibrium averages of 53 and 60 μg/dl, respectively. The exposure for IF was terminated early before his blood lead had achieved equilibrium. No response in blood lead was seen for subject SW whose supplement was 300 μg/day.

11.4.2.2.2 Stuik study. Stuik (1974) administered lead acetate in two dose levels (20 and 30 μg/kg·day) to volunteers. The study was conducted in two phases. The first phase was conducted for 21 days during February-March, 1973. Five males and five females aged 18-26 were exposed to a daily dose of 20 μg Pb^{2+}/kg. Five males served as controls. In the second phase, five females received 20 μg Pb^{2+}/kg and five males received 30 μg Pb^{2+}/kg. Five females served as controls. Pre-exposure values were established during the week preceding the exposures in both phases. Blood lead levels were determined by Hessel's method.

The results of phase I for blood lead levels are presented in Figure 11-24. Blood lead levels appeared to achieve an equilibrium after 17 days of exposure. Male blood lead levels went from 20.6 to 40.9 μg/g while females went from 12.7 to 30.4 μg/g. The males seemed to respond more to the same body weight dose.

In phase II, males were exposed to a higher lead dose (30 μg/kg·day). Figure 11-25 displays these results. Male blood lead rose higher than in the first study (46.2 versus 40.9 μg/g); furthermore, there was no indication of a leveling off. Females also achieved a higher blood lead level (41.3 versus 30.4 μg/dl), which the author could not explain. The pre-exposure level, however, was higher for the second phase than the first phase (12.7 versus 17.3 μg/g).

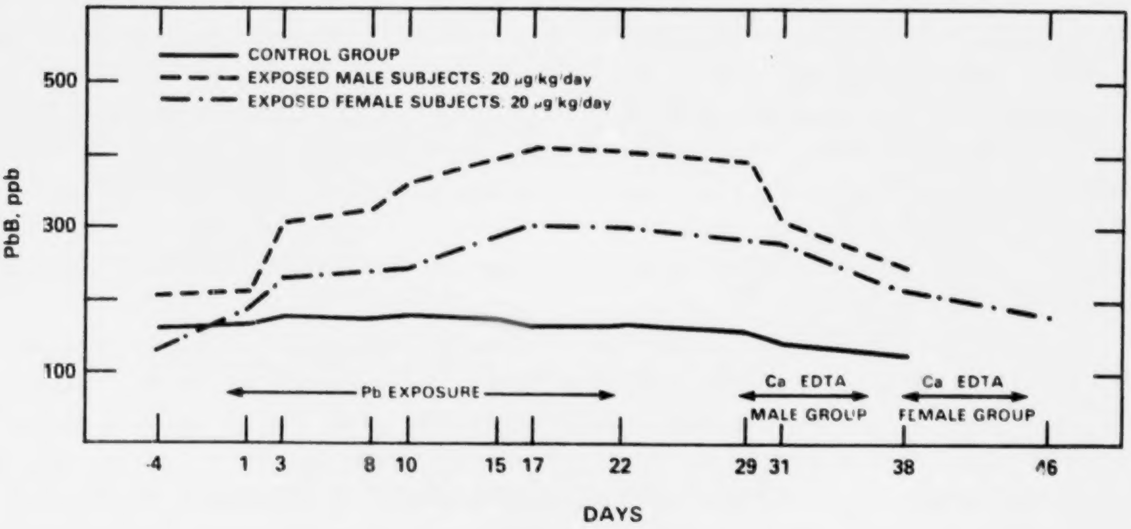


Figure 11-24. Average PbB levels, Exp. I.

Source: Stuik (1974).

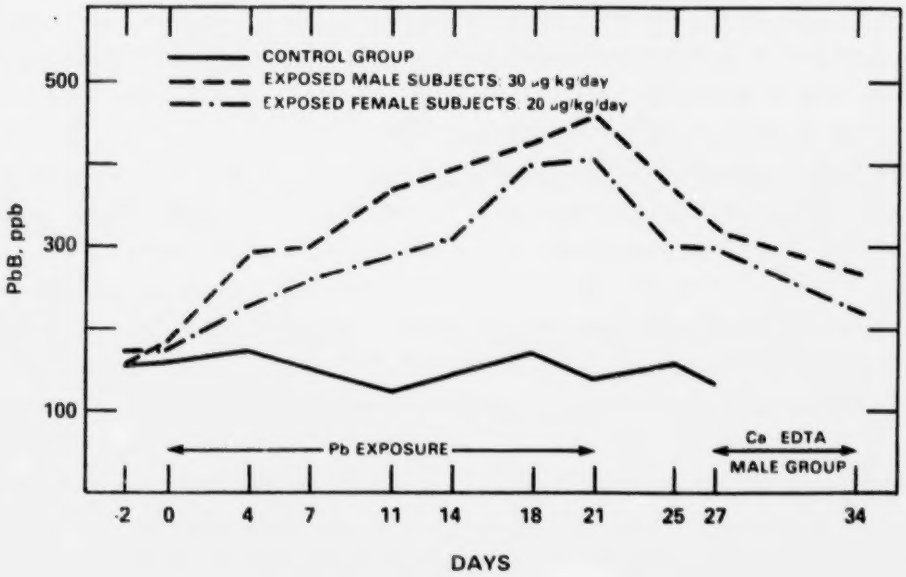


Figure 11-25. Average PbB levels, Exp. II.

Source: Stuik (1974).

11.4.2.2.3 Cools study. Cools et al. (1976) extended the research of Stuik (1974) by randomly assigning 21 male subjects to two groups. The experimental group was to receive a 30 µg/kg body weight dose of oral lead acetate for a period long enough to achieve a blood lead level of 30.0 µg/g, when the lead dose would be adjusted downward to attempt to maintain the subjects at a blood lead level of 40.0 µg/g. The other group received a placebo.

In the pre-exposure phase, blood lead levels were measured three times, while during exposure they were measured once a week, except for the first three weeks when they were determined twice a week. Blood lead was measured by flame AAS according to the Westerlund modification of Hessel's method.

Pre-exposure blood lead values for the 21 volunteers averaged 172 ppb. The effect of ingestion of lead acetate on blood lead is displayed in Figure 11-26. After 7 days, mean blood lead levels had increased from 17.2 to 26.2 µg/g. The time to reach a blood lead level of 35.0 µg/g took 15 days on the average (range 7-40 days).

11.4.2.2.4 Schlegel study. Schlegel and Kufner (1979) report an experiment in which two subjects received daily oral doses of 5 mg Pb^{2+} as an aqueous solution of lead nitrate for 6 and 13 weeks, respectively. Blood and urine samples were taken. Blood lead uptake (from 16-60 µg/dl in 6 weeks) and washout were rapid in subject HS, but less so in subject GK (from 12-29 µg/dl in 6 weeks). Time series data on other heme system indicators (FEP, ALA-D, ALA-U, coproporphyrin III) were also reported.

11.4.2.2.5 Chamberlain study. This study (Chamberlain et al., 1978) was described in Section 11.4.1, and in Chapter 10. The ingestion studies on six subjects showed that the gut absorption of lead was much higher when lead was ingested between meals. There were also differences in absorption of lead chloride and lead sulfide.

11.4.2.3 Inadvertent Lead Ingestion from Lead Plumbing.

11.4.2.3.1 Early studies. Although the use of lead piping has been largely prohibited in recent construction, occasional episodes of poisoning from this lead source still occur. These cases most frequently involve isolated farms or houses in rural areas, but a surprising urban episode was revealed in 1972 when Beattie et al. (1972a,b) showed the seriousness of the situation in Glasgow, Scotland, which had very pure, but soft, drinking water as its source. The researchers demonstrated a clear association between blood lead levels and inhibition of the enzyme ALA-D in children living in houses with (1) lead water pipes and lead water tanks, (2) no lead water tank but with more than 60 ft of lead piping, and (3) less than 60 ft of lead piping. The mean lead content of the water as supplied by the reservoir was 17.9 µg/l; those taken from the faucets of groups 1, 2, and 3 were 934, 239, and 108 µg/l, respectively.

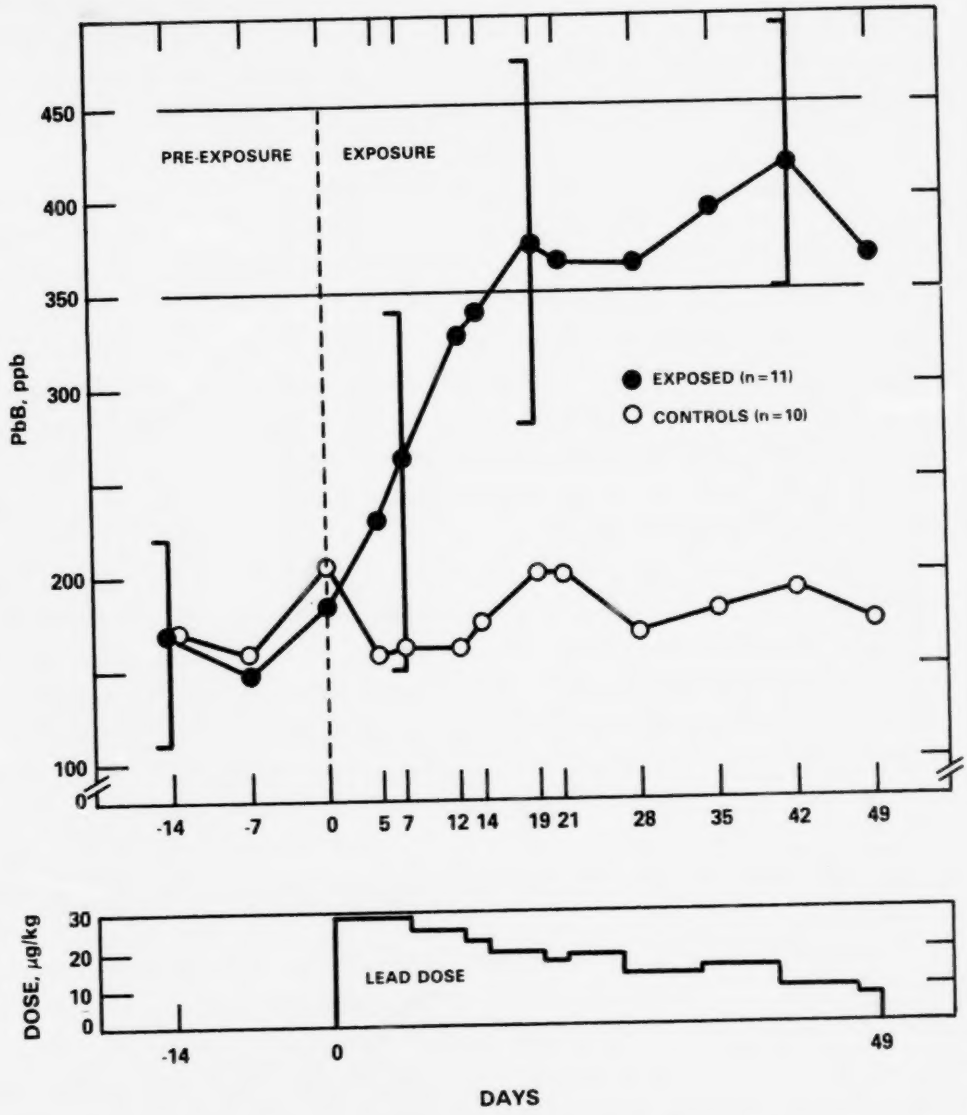


Figure 11-26. Lead in blood (mean values and range) in volunteers. In the lower curve the average daily lead dose of the exposed group is shown.

Source: Cools et al. (1976).

Another English study (Crawford and Crawford, 1969) showed a clear difference between the bone lead contents of the populations of Glasgow and London, the latter having a hard, nonsolvent water supply. In a study of 1200 blood donors in Belgium (De Graeve et al., 1975), persons from homes with lead piping and supplied with corrosive water had significantly higher blood lead levels.

11.4.2.3.2 Moore studies. Moore and colleagues have reported on several studies relating blood lead levels to water lead levels. Moore (1977) studied the relationship between blood lead level and drinking water lead in residents of a Glasgow tenement. The tenement was supplied with water from a lead-lined water tank carried by lead piping. Water samples were collected during the day. Comparative water samples were collected from houses with copper pipes and from 15 lead-plumbed houses. Blood samples were taken wherever possible from all inhabitants of these houses. The data indicated that if a house has lead-lined pipes, it is almost impossible to reach the WHO standard for lead in water (100 μg/l). Linear regression equations relating blood lead levels to first flush and running water lead levels are in Tables 11-51 and 11-52 in Section 11.4.2.4.

Moore (1977) also reported the analysis of blood lead and water lead data collected over a four-year period for different sectors of the Scottish population. The combined data showed consistent increases in blood lead levels as a function of first draw water lead, but the equation was nonlinear at the higher range. The water lead values were as high as 2000 μg/l. The fitted regression equation for the 949 subjects is in Table 11-51 in Section 11.4.2.4.

Moore et al. (1981a,b) reported a study of the effectiveness of control measures for plumbosolvent water supplies. In autumn and winter of 1977, they studied 236 mothers aged 17-37 in a postnatal ward of a hospital in Glasgow with no historical occupational exposure. Blood lead and tap water samples from the home were analyzed for lead by AAS under a quality control program.

A skewed distribution of blood lead levels was obtained with a median value of 16.6 μg/dl; 3 percent of the values exceeded 41 μg/dl. The geometric mean was 14.5 μg/dl. A curvilinear relationship between blood lead level and water lead level was found. The log of the maternal blood lead varied as the cube root of both first flush and running water lead concentrations. In Moore et al. (1979), further details regarding this relationship are provided. Figure 11-27 presents the observed relationship between blood lead and water lead.

In April, 1978, a closed loop lime dosing system was installed. The pH of the water was raised from 6.3 to 7.8. Before the treatment, more than 50 percent of random daytime water samples exceeded 100 μg/l, the WHO standard. After the treatment was implemented, 80 percent of random samples were less than 100 μg/l. It was found, however, that the higher pH was not maintained throughout the distribution system. Therefore, in August, 1980, the pH was raised

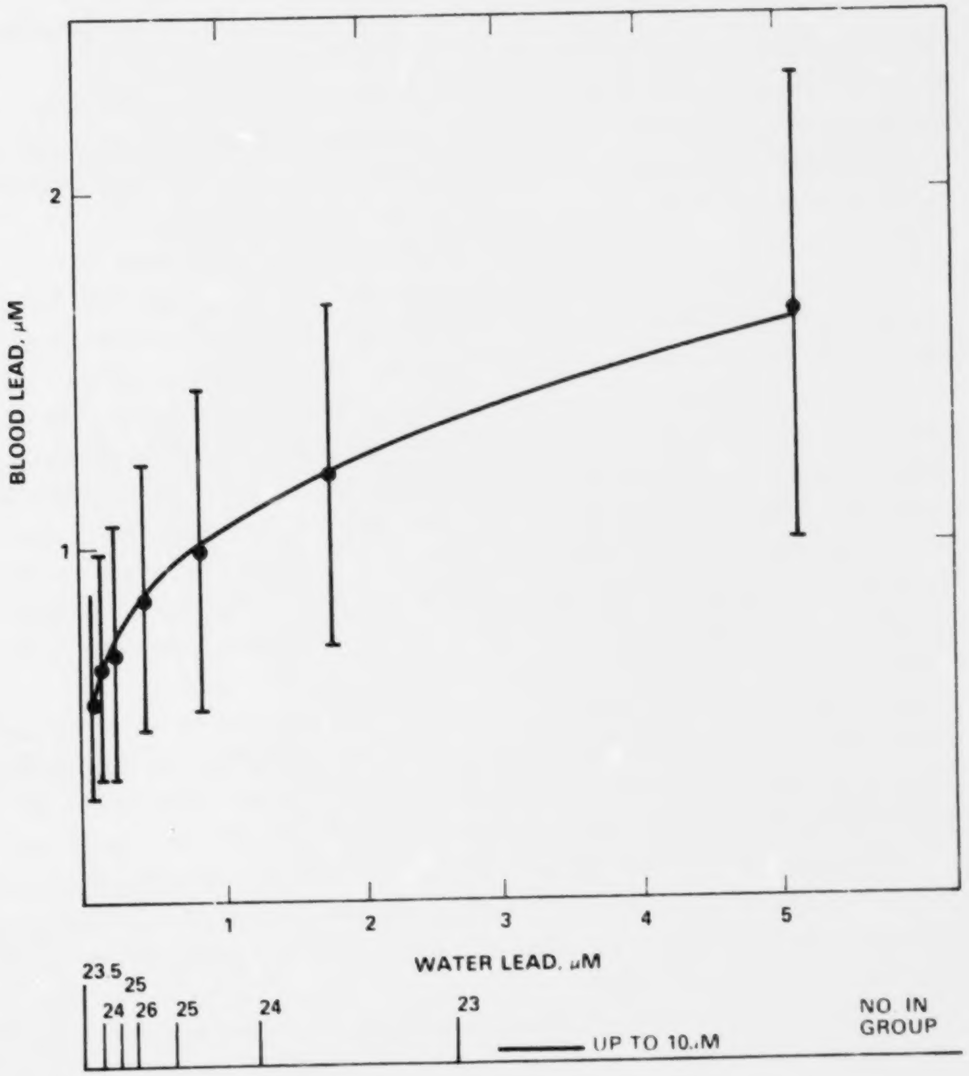


Figure 11-27. Cube root regression of blood lead on first flush water lead. This shows mean ± S.D. of blood lead for pregnant women grouped in 7 intervals of first flush water lead.

Source: Moore et al. (1979).

to 9 at the source, thereby maintaining the tap water at 8. At this time, more than 95 percent of random daytime samples were less than 100 µg/l.

In the autumn and winter of 1980, 475 mothers from the same hospital were studied. The median blood lead was 6.6 µg/dl and the geometric mean was 8.1 µg/dl. Comparison of the frequency distributions of blood lead between these two blood samplings show a remarkable drop. No other source of lead was thought to account for the observed change.

Sherlock et al. (1984) report that water treatment produced a sharp fall in water lead concentrations and a decrease in the median blood lead concentrations from 21 to 13 µg/dl.

11.4.2.3.3 Thomas study. Thomas et al. (1979) studied women and children residing on two adjacent housing estates. One estate was serviced by lead pipes for plumbing while the other was serviced by copper pipe. In five of the homes in the lead pipe estate, the lead pipe had been replaced with copper pipe. The source water is soft, acidic, and lead-free.

Water samples were collected from the cold tap in the kitchen in each house on three occasions at two-week intervals. The following water samples were collected: daytime - first water out of tap at time of visit; running - collected after tap ran moderately for 5 minutes after the daytime sample; and first flush - first water out of tap in morning (collected by residents). Lead was analyzed by a method (unspecified in report) that was reportedly under quality control.

Blood samples were collected from adult females (2.5 ml venipuncture) who spent most of the time in the home and from the youngest child (capillary sample). Blood samples were analyzed for lead by a quality-controlled unspecified method. Blood lead levels were higher in the residents of the lead estate homes than in the residents of the copper estate homes. Median levels for adult females were 39 and 14.5 µg/dl for the lead and copper estate homes, respectively. Likewise, children's blood lead levels were 37 and 16.6 µg/dl, respectively. Water lead levels were substantially higher for the lead estate than for the copper estate. This was true for all three water samples.

The researchers then monitored the effectiveness of replacing the lead pipe on reducing both exposure to lead in drinking water and, ultimately, blood lead levels. This monitoring was done by examining subsamples of adult females for up to 9 months after the change was implemented. Water lead levels became indistinguishable from those found in the copper estate homes. Blood lead levels declined about 30 percent after 3-4 months and 50 percent at 6 and 9 months. At 6 months the blood lead levels reached those of women living in the copper estates. A small subgroup of copper estate females was also followed during this time. No decline was noted among them. Therefore, it was very likely that the observed reduction in blood lead levels among the other women was due to the changed piping.

The researchers then analyzed the form of the relationship between blood lead levels and water lead levels. They tried several different shapes for the regression line. Curvilinear models provided better fits. Figure 11-28 depicts the scatter diagram of blood lead and water lead. An EPA analysis of the data is in Table 11-51 in Section 11.4.2.4.

A later publication by Thomas (1980) extended his earlier analysis. This more extensive analysis was limited to lead estate residents. Subjects who did not consume the first drawn water from the tap had significantly lower blood lead levels than those who did (10.4 µg/dl difference). No gradient was noted in blood lead levels with increasing water consumption. Furthermore, no gradient in blood lead levels was noted with total beverage consumption (tea ingestion frequency).

11.4.2.3.4 Worth study. In Boston, Massachusetts, an investigation was made of water distribution via lead pipes. In addition to the data on lead in water, account was taken of socioeconomic and demographic factors as well as other sources of lead in the environment (Worth et al., 1981). Participants, 771 persons from 383 households, were classified into age groups of less than 6, 6-20, and greater than 20 years of age for analysis. A clear association between water lead and blood lead was apparent (Table 11-48). For children under 6 years of age, 34.6 percent of those consuming water with lead above the U.S. standard of 50 µg/l had a blood lead value greater than or equal to 35 µg/dl, whereas only 17.4 percent of those consuming water within the standard had blood lead values of greater than or equal to 35 µg/dl.

Worth et al. (1981) have published an extensive regression analysis of these data. Blood lead levels were found to be significantly related to age, education of head of household, sex, and water lead exposure. Of the two types of water samples taken, standing grab sample and running grab sample, the former was shown to be more closely related to blood lead levels than the latter. Regression equations are given in Tables 11-51 and 11-52 in Section 11.4.2.4.

11.4.2.4 Summary of Dietary Lead Exposures, Including Water. It is difficult to obtain accurate dose-response relationships between blood lead levels and lead levels in food or water. Dietary intake must be estimated by duplicate diets or fecal lead determinations. Water lead levels can be determined with some accuracy, but the varying amounts of water consumed by different individuals add to the uncertainty of the estimated relationships.

Studies relating blood lead levels to dietary lead intake are compared in Table 11-49. Two studies had subjects with relatively high dietary lead intakes. In the Sherlock et al. (1982) study, 10 of 31 subjects had lead intake levels greater than 300 µg/day. In the United Kingdom Central Directorate study (1982), 12 of 110 subjects had levels greater than 300 µg/day. These concentrations are high enough that the slope is clearly lower in this range than it is in the 0-100 µg/day range. The estimates of slopes for the cube root models may be overestimates in the low range (0-100 µg/day) for the reasons discussed in section 11.4.

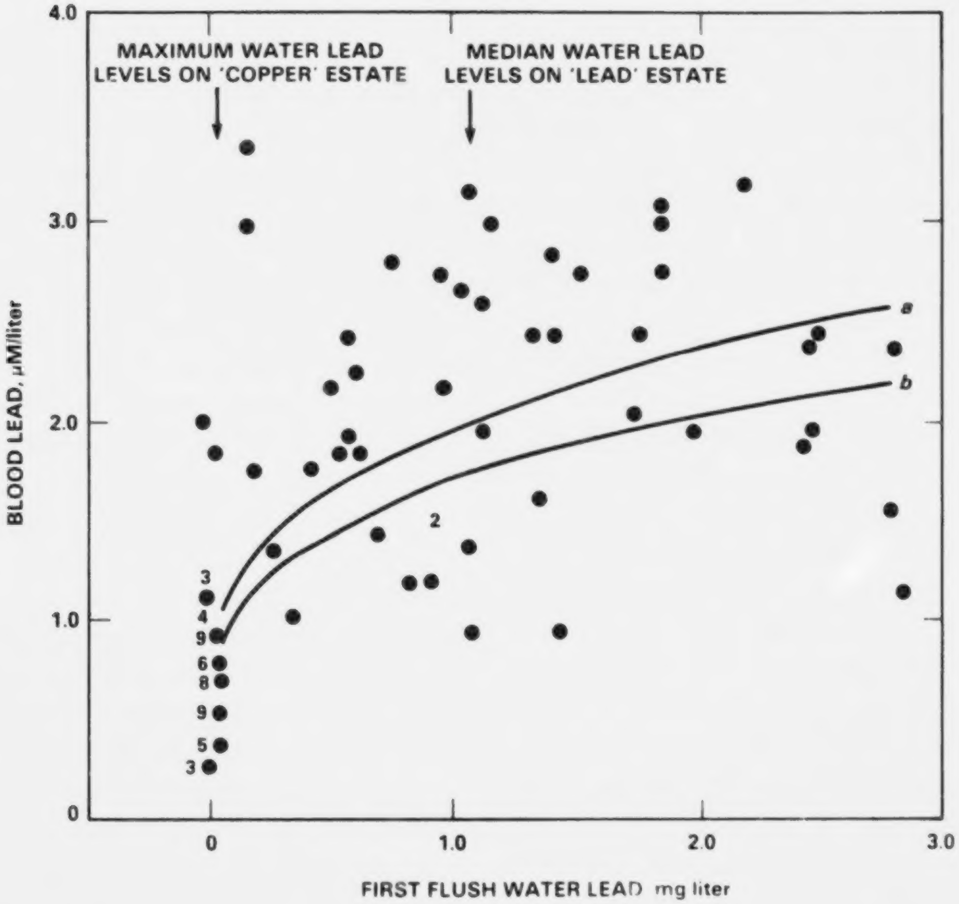


Figure 11.28. Relation of blood lead (adult female) to first flush water lead in combined estates. (Numbers are coincidental points: 9 = 9 or more.) Curve *a*, present data; curve *b*, data of Moore *et al.* (1979).

TABLE 11-48. BLOOD LEAD LEVELS OF 771 PERSONS IN RELATION TO LEAD CONTENT OF DRINKING WATER, BOSTON, MA

Blood lead levels, μg/dl	Persons consuming water (standing grab samples)				
	<50 μg Pb/l		≥50 μg Pb/l		
	No.	Percent	No.	Percent	Total
<35	622	91	68	77.3	690
≥35	61	9	20	22.7	81
Total	683	100	88	100.0	771

$\chi^2 = 14.35$; df = 1.

$p < 0.01$.

Source: Worth et al. (1981).

Conversely, the linear equation is probably an underestimate. The slope from the Ryu study was estimated directly from changes in infants and is the best estimate available. The estimates for adults are more accurately estimated from the experimental studies.

The experimental studies are summarized in Table 11-50. Most of the dietary intake supplements were so high that many of the subjects had blood lead concentrations much in excess of 30 μg/dl for a considerable part of the experiment. Blood lead levels thus may not completely reflect lead exposure, due to the previously noted nonlinearity of blood lead response at high exposures. The slope estimates for adult dietary intake are about 0.02 μg/dl increase in blood lead per μg/day intake, but consideration of blood lead kinetics may increase this value greatly. Such values are a bit lower than those estimated from the adult population studies extrapolated to typical dietary intakes in Table 11-49, about 0.05 μg/dl per μg/day. The value for infants is much larger.

The studies relating first flush and running water lead levels to blood lead levels are in Tables 11-51 and 11-52, respectively. Many of the authors chose to fit cube root models to their data, although polynomial and logarithmic models were also used. Unfortunately, the form of the model greatly influences the estimated contributions to blood lead levels from relatively low water lead concentrations. As indicated in section 11.4, the models producing high estimated contributions are the cube root models and the logarithmic models. All others are polynomial models, either linear, quadratic, or cubic. The slopes of these models tend to be relatively constant at the origin.

TABLE 11-49. STUDIES RELATING BLOOD LEAD LEVELS (μg/dl) TO DIETARY INTAKES (μg/day)

Study	Analysis	Model	R^2	Model D.F.	Estimated blood lead at 0 H_2O Pb	Predicted blood lead contribution (μg/dl) for a given dietary intake (μg/d)			Slope from 100 to 200 μg/d, μg/dl per μg/d
						100	200	300	
Sherlock et al. (1982) study of 31 adult women in Ayr	Sherlock et al. (1982)	$PbB = -1.4 + 3.6 \sqrt[3]{PbD}$	0.52	2	-1.4	16.7	21.1	24.1	0.034
Sherlock et al. (1982) study of infants in Ayr combined with U.K. Central Directorate Study	Sherlock et al. (1982)	$PbB = 2.5 + 5.0 \sqrt[3]{PbD}$	-	2	2.5	23.2	29.2	33.5	0.060
U.K. Central Directorate (1982) Study of infants in Glasgow	U.K. Central Directorate on Environmental Pollution (1982)	$PbB = 17.1 + 0.056(PbD)$ or	0.39	2	17.1	5.6	11.2	16.8	0.056
		$PbB = 3.9 + 4.6 \sqrt[3]{PbD}$	0.43	2	3.9	21.4	26.9	30.8	0.053
Ryu et al. (1983) study of infants	EPA	$PbB = A + 0.16PbD$	-	1	-	16.0	32.0	48.0	0.16

TABLE 11-50. STUDIES INVOLVING BLOOD LEAD LEVELS (μg/dl) AND EXPERIMENTAL DIETARY INTAKES

Study	Subjects	Exposure	Form of lead	Blood lead		Slope,* μg/dl per μg/d
				Initial	Final	
Stuik (1974) Study I	5 adult male students	20 μg/kg/day - 21 d.	Lead acetate	20.6	40.9	0.017**,***
	5 adult female students	20 μg/kg/day - 21 d.	Lead acetate	12.7	30.4	0.018**,***
	5 adult male students	Controls - 21 d.	Placebo	20.6	18.4	-
Study II	5 adult female students	20 μg/kg/day	Lead acetate	17.3	41.3	0.022
	5 adult male students	30 μg/kg/day	Lead acetate	16.1	46.2	0.014
	5 adult female students	Controls	Placebo	~17.0	~17.0	-
Cools et al. (1976)	11 adult males	30 μg/kg/day ~7 days	Lead acetate	17.2	26.2	0.027***
	10 adult males	Controls	Placebo		~19.0	-
Schlegel and Kufner (1979)	1 adult male	50 μg/kg/day - 6 wk.	Lead nitrate	16.5	64.0	0.014
	1 adult male	70 μg/kg/day -13 wk.	Lead nitrate	12.4	30.4	0.004****
Gross (1979) analysis of Kehoe's experiments	1 adult male	300 μg/day	Lead acetate		-1	[0]
	1 adult male	1000 μg/day	Lead acetate		+17	0.017
	1 adult male	2000 μg/day	Lead acetate		+33	0.016
	1 adult male	3000 μg/day	Lead acetate		+19	0.006*****

* Exposure (μg/d) = Exposure (μg/kg/day) x 70 kg for males, 55 kg for females. Slope = (Final - Initial Blood Lead)/Exposure (μg/d).

** Corrected for decrease of 2.2 μg/dl in control males.

*** Assumed mean life 40d. This increases slope estimate for short-term studies. Stuik Study I would be 0.042, 0.044 respectively for males, females.

**** Assumed limited absorption of lead.

***** Removed from exposure before equilibrium.

TABLE 11-51. STUDIES RELATING BLOOD LEAD LEVELS (μg/dl) TO FIRST-FLUSH WATER LEAD (μg/l)

Study	Analysis	Model	R^2	Model D.F.	Estimated blood lead at 0 H_2O Pb	Predicted blood lead contribution (μg/dl) for a given water lead (μg/l)			
						5	10	25	50
Worth et al. (1981) study of 524 subjects in greater Boston. Water leads (standing water) ranged from <13 to 1108 μg/l. Blood leads ranged from 6 to 71.	Worth et al. (1981)	ln (PbB) = 2.729 PbW - 4.699 $(PbW)^2$ + 2.116 $(PbW)^3$ + other terms for age, sex, education, dust (PbW is in mg/l)	0.18	14	20.5	0.3	0.6	1.4	2.7
	EPA	ln (PbB) = ln (.041 PbW - .000219 $(PbW)^2$ + other terms for age, sex, education, dust)	0.18	11	21.1	0.2	0.4	1.0	2.1
Moore et al. (1979) study of 232 mothers at delivery in Glasgow. 17% of the water leads were over 300 μg/l.	Moore et al. (1979)	PbB = 5.81 + 2.73 $(PbW)^{1/3}$	0.44	2	5.8	4.7	5.9	8.0	10.1
Hubermont et al. (1978) study of 70 pregnant women in rural Belgium. Water leads ranged from 0.2 to 1228.5 μg/l. Blood leads ranged from 5.1 to 26.3 μg/dl.	Hubermont et al. (1978)	PbB = 9.62 + 0.756 ℓn (PbW)	0.14	2	8.4*	2.4	3.0	3.7	4.2
U.K. Central Directorate (1982) study of 128 mothers in greater Glasgow. Water leads ranged from under <10 to 1060 μg/l. Blood leads ranged from 2 to 39 μg/dl.	U.K. Cen. Dir. (1982)	PbB = 13.2 + 1.8 $(PbW)^{1/3}$	0.11	2	13.2	3.1	3.9	5.3	6.6
	U.K. Cen. Dir. (1982)	PbB = 18.0 + 0.009 PbW	0.05	2	18.0	0.0	0.1	0.2	0.4
	Lacey et al. (1985)	PbB = 14.0 + 0.062 PbW		2	14.0	0.3	0.6	1.6	3.1
	EPA	ln (PbB) = ln (14.2 + 0.033 PbW - 0.000031 PbW^2)	0.10	3	14.2	0.2	0.3	0.8	1.6
U.K. Central Directorate (1982) study of 126 infants (as above). Blood leads ranged from 1 to 51 μg/dl.	U.K. Cen. Dir. (1982)	PbB = 9.4 + 2.4 $(PbW)^{1/3}$	0.17	2	9.4	4.1	5.2	7.0	8.8
	U.K. Cen. Dir. (1982)	PbB = 17.1 + 0.018 PbW	0.12	2	17.1	0.1	0.2	0.4	0.9
	Lacey et al. (1985)	PbB = 14.0 + .062 PbW		2	14.0	0.3	0.6	1.6	3.1
	EPA	ln (PbB) = ln (14.2 + 0.033 PbW - 0.000031 PbW^2)	0.15	3	12.0	0.2	0.5	1.2	2.4
Thomas et al. (1979) study of 115 adult Welsh females. Water leads ranged from <10 to 2800 μg/dl. Blood leads ranged from 5 to 65 μg/dl.	EPA	ln (PbB) = [14.9 + 0.041 PbW - 0.000012 $(PbW)^2$]	0.61	3	14.9	0.2	0.4	1.0	2.0
Moore (1977) study of 75 residents of a Glasgow tenement	Moore (1977)	PbB = 15.7 + 0.015 PbW	0.34	2	15.7	0.1	0.2	0.4	0.8
Pocock et al. (1983) study of 7735 men aged 40-59 in Great Britain. Water leads restricted to <100 μg/l.	Pocock et al. (1983)	PbB = 14.48 + 0.062 PbW		2	14.5	0.3	0.6	1.6	3.1
Moore (1984) study of 568 mothers in Scotland.	Moore (1984)	PbB = 5.5 + 2.63 $(PbW)^{1/3}$	0.59	2	5.5	4.5	5.7	7.7	9.7

*Minimum water lead of 0.2 μg/dl used instead of 0.

TABLE 11-52. STUDIES RELATING BLOOD LEAD LEVELS (μg/dl) TO RUNNING WATER LEAD (μg/l)

Study	Analysis	Model	R^2	Model D.F.	Estimated blood lead at 0 H_2O Pb	Predicted blood lead contribution (μg/dl) for a given water lead (μg/l)			
						5	10	25	50
Worth et al. (1981) study of 524 subjects in greater Boston. Water leads ranged from <13 to 208 μg/dl. Blood leads ranged from 6 to 71.	EPA	ln (PbB) = (0.0425 PbW + other terms for age, sex, education, and dust)	0.153	10	21.3	0.2	0.4	1.1	2.1
Worth et al. (1981) study restricted to 390 subjects aged 20 or older.	U.S. EPA (1980)	$PbB = 14.33 + 2.541 (PbW)^{1/3}$	0.023	2	14.3	4.4	5.4	7.4	9.4
	EPA	ln (PbB) = ln (18.6 + 0.071 PbW)	0.028	2	18.6	0.4	0.7	1.8	3.6
	EPA	ln (PbB) = ln (0.073 PbW + other terms for sex, education, and dust)	0.153	7	18.8	0.4	0.7	1.8	3.7
Worth et al. (1981) study restricted to 249 females ages 20 to 50.	U.S. EPA (1980)	$PbB = 13.38 + 2.487 (PbW)^{1/3}$	0.030	2	13.4	4.3	5.4	7.3	9.2
	EPA	ln (PbB) = ln (17.6 + 0.067 PbW)	0.032	2	17.6	0.3	0.7	1.7	3.4
	EPA	ln (PbB) = (0.067 PbW + other terms for education and dust)	0.091	6	17.6	0.3	0.7	1.7	3.4
U.K. Central Directorate (1982) study of 128 mothers in greater Glasgow. Water leads ranged from under 20 to 720 μg/l. Blood leads ranged from 1 to 39 μg/dl.	U.K. Cen.Dir.(1982)	$PbB = 12.8 + 1.8 (PbW)^{1/3}$	0.12	2	12.8	3.1	3.9	5.3	6.6
	U.K. Cen.Dir.(1982)	PbB = 18.1 + 0.014 PbW	0.06	2	18.1	0.1	0.4	0.4	0.7
	EPA	$\ln (PbB) = \ln (13.4 + 0.071\ PbW - 0.000104\ PbW^2)$	0.16	3	13.4	0.4	0.7	0.7	3.3
U.K. Central Directorate (1982) study of 126 infants (as above). Blood leads ranged from 1 to 51 μg/dl.	U.K. Cen.Dir.(1982)	$PbB = 7.6 + 2.3 (PbW)^{1/3}$	0.22	2	7.6	3.9	5.0	6.7	8.5
	U.K. Cen.Dir.(1982)	PbB = 16.7 + 0.033 PbW	0.12	2	16.7	0.2	0.3	0.8	1.6
	EPA	$\ln (PbB) = \ln (12.3 + 0.068\ PbW - 0.000056\ PbW^2)$	0.20	3	12.3	0.3	0.7	1.7	3.3
Moore (1977) study of 75 residents of a Glasgow tenement.	Moore (1977)	PbB = 16.6 + 0.02 PbW	0.27	2	16.6	0.1	0.2	0.5	1.0
Sherlock et al. (1982) study of 114 adult women. Blood leads ranged <5 to >61 μg/dl. Kettle water leads ranged from <10 to >2570 μg/l.	Sherlock et al. (1982)	$PbB = 4.7 + 2.78 (PbW)^{1/3}$	0.56	2	4.7	4.8	6.0	8.1	10.2
	EPA	$\ln (PbB) = \ln (11.5 + 0.033\ PbW - 0.00001\ PbW^2)$	0.55	3	11.5	0.2	0.3	0.8	1.6
Sherlock et al. (1984) follow-up study.	Sherlock et al. (1984)	$PbB = 5.6 + 2.62 (PbW)^{1/3}$	0.65	2	5.6	4.5	5.6	7.7	9.7

The problem of determining the most appropriate model(s) at low water lead levels (0-25 μg/l) is extremely difficult. Most data sets estimate a relationship that is primarily based on water lead levels of 50-2000 μg/l, and the problem becomes essentially a low-dose extrapolation problem. The only study which estimates the relationship based primarily on lower water lead levels (<100 μg/l) is the Pocock et al. (1983) study. The data from this study, as well as the authors themselves, suggest that in this lower range of water lead levels, the relationship is linear. Furthermore, the contributions to blood lead levels estimated from this study are quite consistent with the polynomial models from the other first-flush water lead studies, such as Worth et al. (1981), United Kingdom Central Directorate on Environmental Pollution (1982), and Thomas et al. (1979). For these reasons the Pocock et al. (1983) slope of 0.06 is our best estimate for first-flush water lead studies. The slopes for running water lead studies are about 1.5 to 2.0 times as large. The possibility does exist, however, that the higher initial slopes from the cube-root and logarithmic models are correct.

11.4.3 Studies Relating Lead in Soil and Dust to Blood Lead

The relationship of exposure to lead contained in soil and house dust, and the amount of lead absorbed by humans, particularly children, has been the subject of scientific investigation for some time (Duggan and Williams, 1977; Barltrop, 1975; Creason et al., 1975; Barltrop et al., 1974; Roberts et al., 1974; Sayre et al., 1974; Ter Haar and Aronow, 1974; Fairey and Gray, 1970). Duggan and Williams (1977) published an assessment of the risk of increased blood lead resulting from the ingestion of lead in dust. Some of these studies have been concerned with the effects of such exposures (Barltrop, 1975; Creason et al., 1975; Barltrop et al., 1974; Roberts et al., 1974; Fairey and Gray, 1970); others have concentrated on the means by which the lead in soil and dust becomes available to the body (Sayre et al., 1974; Ter Haar and Aronow, 1974; Brunekreef et al., 1983).

11.4.3.1 Omaha, Nebraska Studies. The Omaha studies were described in Section 11.4.1.7. Soil samples were 2-inch cores halfway between the building and the lot line. Household dust was collected from vacuum cleaner bags. The following analysis was provided courtesy of Dr. Angle. The model is also described in Section 11.4.1.8, and provided the coefficients and standard errors shown in Table 11-53.

11.4.3.2 Stark Study. Stark et al. (1982) used a large-scale lead screening program in New Haven, Connecticut, during 1974-77 as a means of identifying study subjects. The screening program had blood lead levels on 8289 children, ages 1-72 months, that represented about 80 percent of the total city population in that age group. From this initial population, a much smaller subset of children was identified for a detailed environmental exposure study. Using the classifying criteria of residential stability and repeatable blood lead levels (multiple

TABLE 11-53. COEFFICIENTS AND STANDARD ERRORS FOR OMAHA STUDY MODEL

Factor	Coefficient	Asymptotic Standard Error
Intercept (μg/dl)	15.67	0.398
Air lead (μg/m^3)	1.92	0.600
Soil lead (mg/g)	6.80	0.966
House dust (mg/g)	7.18	0.900

Multiple $R^2 = 0.198$
Sample size = 1075
Residual standard deviation = 0.300 (geometric standard deviation = 1.35)

measurements fell into one of three previously defined blood lead concentration categories), a potential study population of 784 was identified. Change of residence following identification and refusal to let sanitarians make inspections resulted in 407 children being dropped; the final study population contained 377 children.

With the exception of dietary lead intake, each child's potential total external lead exposure was assessed. Information was obtained on lead in air, house dust, interior and exterior paint, and soil near and far from the home. A two percent sample of homes with children having elevated lead levels had tap water lead levels assessed. No water lead levels above the public health service standard of 50 μg/l were found. Socioeconomic variables were also obtained.

For all children in the study, micro blood samples were taken and analyzed for lead by AAS with Delves cup attachment. Blood lead values were found to follow a lognormal distribution. Study results were presented using geometric means and geometric standard deviation. Among the various environmental measurements a number of significant correlation coefficients were observed. However, air lead levels were independent of most of the other environmental variables. Environmental levels of lead did not directly follow socioeconomic status. Most of the children, however, were in the lower socioeconomic groups.

Multiple regression analyses were performed by Stark et al. (1982) and by EPA*, using all 926 blood lead measurements. Stark and coworkers derived a log-log model with $R^2 = 0.11$, and no significant effects of race or age were found. EPA fitted a linear exposure model in logarithmic form with results shown in Table 11-54. Significant differences among age groups were

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*NOTE: The term EPA analyses refers to calculations done at EPA. A brief discussion of the methods used is contained in Appendix 11-B; more detailed information is available at EPA upon request.

TABLE 11-54. MULTIPLE REGRESSION MODELS FOR BLOOD LEAD OF CHILDREN IN NEW HAVEN, CONNECTICUT, SEPTEMBER 1974 - FEBRUARY 1977

Covariate	Regression Coefficients and Standard Errors Ages 0-1 yr	Ages 2-3 yr	Ages 4-7 yr
Summer - winter	6.33 ± 2.11*	3.28 ± 1.30*	2.43 ± 1.38*
Dust, μg/g	0.00402 ± 0.00170*	0.00182 ± 0.00066*	0.00022 ± 0.00077
Housekeeping quality	4.38 ± 2.02*	1.75 ± 1.17	-1.61 ± 1.12
Soil near house, μg/g	0.00223 ± 0.00091*	-0.00016 ± 0.00042	0.00060 ± 0.00041
Soil at curb, μg/g	0.00230 ± 0.00190	0.00203 ± 0.00082*	0.00073 ± 0.00079
Paint, child's bedroom	0.0189 ± 0.0162	0.0312 ± 0.0066*	0.0110 ± 0.0064*
Paint outside house	-0.0023 ± 0.0138	0.0200 ± 0.0069*	0.0172 ± 0.0067*
Paint quality	0.89 ± 1.71	3.38 ± 0.96*	4.14 ± 1.15*
Race = Black	2.16 ± 2.05	0.07 ± 1.09	5.81 ± 1.00*
Residual standard deviations	0.1299	0.0646	0.1052
Multiple R^2	0.289	0.300	0.143
Sample size (blood samples)	153	334	439

*Significant positive coefficient, one-tailed $p < 0.05$.

noted, with considerably improved predictability ($R^2 = 0.29, 0.30, 0.14$ for ages 0-1, 2-3, and 4-7). Sex was not a significant variable, but Race = Black was significant at ages 4-7. Air lead did not significantly improve the fit of the model when other covariates were available, particularly dust, soil, paint, and housekeeping quality. However, the range of air lead levels was small (0.7-1.3 μg/m^3) and some of the inhalation effect may have been confounded with dust and soil ingestion. Seasonal variations were important at all ages.

EPA analyses of data from children in New Haven (Stark et al., 1982) found substantial evidence for dust and soil lead contributions to blood lead, as well as evidence for increased blood lead due to decreased household cleanliness. These factors are somewhat correlated with each other, but the separate roles of increased concentration and cleanliness could be distinguished. Overall dust, soil, and paint lead levels were not presented in the published papers, but data presented by year of housing construction indicate that meaningful lead exposures were present. Geometric mean dust lead levels varied from 239 ppm for houses built in

1960-1969 to 756 ppm for those built in 1910-1919. Soil lead levels varied from 131 ppm to 1273 ppm for 1970-1977 and 1920-1929, respectively.

11.4.3.3 The Silver Valley/Kellogg Idaho Study. The Silver Valley/Kellogg Idaho study was discussed in section 11.4.1.6. Yankel et al. (1977) showed that lead in both soil and dust was independently related to blood lead levels. In their opinion, 1000 µg/g soil lead exposure was cause for concern. Walter et al. (1980) showed that children aged 3 through 6 showed the strongest relationship between soil lead and blood lead, but 2-year-olds and 7-year-olds also had a significant relationship (Table 11-29). The slope of 1.1 for soil lead (1000 µg/g) to blood lead (µg/dl) represents an average relationship for all ages.

The Silver Valley-Kellogg Idaho study also gave some information on house dust lead, although this data was less complete than the other information. Regression coefficients for these data are in Tables 11-29 and 11-30. In spite of the correlation of these predictors, significant regression coefficients could be estimated separately for these effects.

11.4.3.4 Blood Lead Levels of Dutch City Children. Brunekreef et al. (1983) reported on a very extensive study on blood lead and environmental variables in native Dutch children 4-6 years old. Three hundred seventy-one children participated in the blood lead survey and 195 children in the environmental study as well. The environmental evaluation was carried out in April-June 1981 in the cities of Rotterdam, the Hague, and Zoetermeer. Blood was sampled by venipuncture. The environmental variables included:

In the home of each child:
- lead in drinking water (one first-draw sample)
- lead deposition indoors, using 2 greased deposition plates per home and an averaging time of 4 weeks
- lead in floor dust, using a special vacuum cleaner to take 2 duplicate samples 4 weeks apart
- lead in 0-5 cm top soil in gardens, if present

In living area:
- lead deposition outdoors on 5-10 spots per area with an averaging time of 4 weeks
- lead in street dust using the vacuum cleaner method, taking 30-40 duplicate samples per area on 2 occasions 4 weeks apart

In the classroom/school:
- lead in drinking water (one running sample)
- lead deposition indoors, applying 2 plates in 2 classrooms per school with an averaging time of 4 weeks
- lead in floor dust, taking 2 duplicate samples in 2 different classrooms per school, 4 weeks apart
- lead in playground dust, using the vacuum cleaner method to take 4 duplicate samples on two occasions 4 weeks apart
- lead in 0-5 cm top soil in playground
- lead on dominant hand of child, after playing outdoors for at least 30 minutes in school playground on a dry day.

Resulting blood lead levels and environmental lead measurements are shown in Tables 11-55 to 11-58.

Multiple regression analyses were done by Brunekreef et al. in logarithmic rather than linear form. The equation is as follows.

$$\begin{aligned}\ln \text{PbB} = {} & 1.882 + 0.163^{c} \ln (\text{lead deposition outdoors}) - 0.003^{b} (\text{year of construction} - 1900) + 0.135^{b} (\text{hand dirtiness}) - 0.380^{d} (\text{milk consumption}) + 0.116^{b} \\ & (\text{presence of pets}) + 0.106^{a} (\text{mouthing behavior}) - 0.069^{b} (\text{number of rooms})\end{aligned}$$

$^{a}p < 0.01$. $^{b}p < 0.005$. $^{c}p < 0.001$. $^{d}p < 0.0001$. (11-19)

Multiple regression analysis for combined inner city and suburban populations give the following: $n = 193$, $R^2 = 0.519$, F-total = 28.5.

Lead deposition outdoors was an important factor, but only in the combined sample, so confounding cannot be ruled out. This appears, however, to be the single most important environmental source, particularly in conjunction with hand dirtiness and with mouthing behavior. Further analyses of these data are proposed. The difference of about 2 µg/dl between city and suburban children (adjusted for all other covariates) can hardly be attributed to direct inhalation of ambient air lead which differs slightly from city to suburb (0.12-0.13 µg/m^3), and hence must be attributed to other pathways. The large coefficient for milk reflects the known importance of calcium in lead metabolism and is also related to mouthing behaviors, including pica. The presence of pets probably increases the exposure to dirt. This study thus corroborates the importance of various non-inhalation pathways for lead in children, particularly the dust-hand-mouth pathway.

Dr. Brunekreef has (personal communication, February 8, 1984) fitted his data on Dutch children to a linear model in logarithmic form, as the Environmental Protection Agency has done elsewhere in the present document. The regression coefficients are all statistically significant, and variables are as in his 1983 paper. The logarithmic linear model had variance $s^2 = 0.06272$ and $R^2 = 0.521$; it thus provided an (insignificantly) better description of the data than the original log-log model.

11.4.3.5 Charney Study. Charney et al. (1980) conducted a case control study of children ages 1.5-6 with highly elevated and non-elevated blood lead levels. Cases and controls were initially identified from the lead screening programs of two Rochester, New York, health facilities. Cases were defined as children who had at least two blood lead determinations between 40 and 70 µg/dl and FEP values greater than 59 µg/dl during a 4-month period. Controls were children who had blood lead levels equal to or less than 29 µg/dl and FEP equal to

TABLE 11-55. AIR LEAD LEVELS IN THE ROTTERDAM AREA (BRUNEKREEF ET AL., 1983)

Sampling location	Geometric mean air lead level in $\mu g/m^3$ January-March, 1981	April-June, 1981
Rotterdam (center)	0.27	0.22
Maassluis (upwind suburb)	0.14	0.10

TABLE 11-56. BLOOD LEAD LEVELS IN μg/100 ml FOR CHILDREN WHO PARTICIPATED IN BLOOD SURVEY AND ENVIRONMENTAL SURVEY[a]

City	Number	Geometric mean	Range	Percentile 50	90	98
Rotterdam (center)	54	13.1	7-31	13	19	23
Rotterdam (suburb)	72	8.2	5-15	8	11	14
The Hague	16	11.5	7-21	11	19	21
Zoetermeer	53	7.9	4-15	8	11	14

[a] Difference between city and suburb significant (t-test on arithmetic means; $p < 0.001$).

TABLE 11-57. SCHOOL VARIABLES (ARITHMETIC MEANS) FOR MEASURED LEAD CONCENTRATIONS

City	In drinking water, μg/l	Deposition indoors, $\mu g/m^2/d$	On floors, $\mu g/m^2$	On schoolyard, $\mu g/m^2$	In sandy playground, mg/kg
Rotterdam[a]	6	11.74	100	1120	6
Rotterdam[b]	1	4.29	29	364	5
Zoetermeer[b]	1	4.59	40	337	6

[a] Inner city.

[b] Suburb.

TABLE 11-58. RESULTS OF LEAD MEASUREMENTS REPORTED BY BRUNEKREEF ET AL. (1983)

City	Concentration	Range	n	t-test
Lead deposition outdoors (arithmetic mean, μg/m^2/d)				
Rotterdam[a]	643	394-957	9	p <0.001
Rotterdam[b]	220	144-315	6	p <0.001
The Hague[a]	369	317-439	5	p <0.001
Zoetermeer[b]	125	73-278	10	p <0.001
Lead on streets (geometric mean, μg/m^2)				
Rotterdam[a]	532	168-2304	37	p <0.005
Rotterdam[b]	318	113-1155	36	p <0.005
The Hague[a]	428	81-1339	10	p <0.001
Zoetermeer[b]	126	46-497	21	p <0.001
Lead in garden soil (geometric mean, mg/kg)				
Rotterdam[a]	336		1	
Rotterdam[b]	43	6-184	56	
The Hague[a]	278	35-527	6	p <0.001
Zoetermeer[b]	21	3-75	33	p <0.001
Lead deposition indoors (geometric mean, μg/m^2/d)				
Rotterdam[a]	2.86	0.10-20.86	48	p <0.001
Rotterdam[b]	0.99	0.10-8.40	67	p <0.001
The Hague[a]	4.32	1.95-27.05	13	p <0.001
Zoetermeer[b]	1.51	0.48-4.40	49	p <0.001
Lead on floors (geometric mean, μg/m^2)				
Rotterdam[a]	81	5-740	43	p <0.001
Rotterdam[b]	30	1-410	62	p <0.001
The Hague[a]	58	22-166	11	p <0.025
Zoetermeer[b]	32	3-201	50	p <0.025
Lead in drinking water (geometric mean, μg/l)				
Rotterdam[a]	20	1-126	46	p <0.001
Rotterdam[b]	2	1-50	60	p <0.001
The Hague[a]	21	1-85	16	p <0.001
Zoetermeer[b]	1	1-4	53	p <0.001
Lead on hands (geometric mean, μg/hand)				
Rotterdam[a]	12	1-96	44	p <0.001
Rotterdam[b]	5	1-21	65	p <0.001
Zoetermeer[b]	4	1-18	37	p <0.001

[a] Inner city.

[b] Suburb.

or less than 59 μg/dl. High-level children were selected first and low-level children were group-matched based on age, area of residence, and social class of the family. Home visits were made to gain permission as well as to gather questionnaire and environmental data. Lead analyses of the various environmental samples were done at several different laboratories. No specification was provided regarding the analytical procedures followed.

The matching procedure worked well for age, and mother's educational level and employment status. There were more blacks in the high lead group as well as more Medicaid support. These factors were then controlled in the analysis; no differences were noted between the high and low blood lead groups regarding residence on high traffic density streets (>10,000 vehicles/ day) or census tract of residence.

The two groups differed regarding mean house dust lead levels (1265 μg/sample for high and 123 μg/sample for low). Median values also differed, 149 versus 55 μg/sample. One-third of the children in the low blood lead group had house dust lead samples with more lead than those found in any middle class home previously investigated.

There were considerably greater quantities of lead on the hands of the high blood lead group compared with the low lead group (mean values were 49 and 21 μg/sample, respectively). Hand and house dust lead levels were correlated ($r = 0.25$) but the relationship was not linear. At the low end of the house dust lead values, hand dust was always low but the converse was not true: not every child exposed to high house dust lead had high hand dust levels.

In addition to hand and house dust lead, other factors differentiated the high and low blood lead groups. Although both groups had access to peeling paint in their homes (~2/3), paint lead concentrations exceeding 1 percent were found more frequently in the high as opposed to the low group. Pica (as defined in Chapter Seven) was more prevalent in the high lead group as opposed to the low lead group.

Since the data suggested a multifactorial contribution of lead, a multiple regression analysis was undertaken. The results suggest that hand lead level, house dust lead level, lead in outside soil, and history of pica are very important in explaining the observed variance in blood lead levels.

11.4.3.6 Charleston Studies. In one of the earliest investigations regarding soil lead exposures, Fairey and Gray (1970) conducted a retrospective study of lead poisoning cases in Charleston, South Carolina. Two-inch core soil samples were collected from 170 randomly selected sites in the city and were compared with soil samples taken from homes where 37 cases of lead poisoning had occurred. The soil lead values obtained ranged from 1 to 12,000 μg/g, with 75 percent of the samples containing less than 500 μg/g. A significant relationship between soil lead levels and lead poisoning cases was established; 500 μg/g was used as the cutpoint in the chi-square contingency analysis. Fairey and Gray were the first to examine this complex problem and, although their data support the soil lead hypothesis, the relationship between soil lead and blood lead levels could not be quantified. Furthermore, because no other source of lead was measured, any positive association could have been confounded by additional sources of lead, such as paint or air.

A later study by Galke et al. (1975), in Charleston, used a house-to-house survey to recruit 194 black preschool children. Soil, paint, and air lead exposures, as measured by traffic density, were established for each child. When the population was divided into two groups based on the median soil lead value (585 µg/g), a 5 µg/dl difference in blood lead levels was obtained. Soil lead exposure for this population ranged from 9 to 7890 µg/g. Vehicle traffic patterns were defined by area of recruitment as being high or low. A multiple regression analysis of the data showed that vehicle traffic patterns, lead level in exterior siding paint, and lead in soil were all independently and significantly related to blood lead levels. Using the model described in Appendix 11B, the following coefficients and standard errors were obtained as shown in Table 11-59.

TABLE 11-59. COEFFICIENTS AND STANDARD ERRORS FROM MODEL OF CHARLESTON STUDY

Factor	Coefficient	Asymptotic standard error
Intercept (µg/dl)	25.92	1.61
Pica (1 = eater, 0 = otherwise)	7.23	1.60
Traffic pattern (1 = high, 0 = low)	7.11	1.48
Siding paint (mg/cm^2)	0.33	0.11
Door paint (mg/cm^2)	0.18	0.12
Soil lead (mg/g)	1.46	0.59

Multiple R^2 = 0.386
Residual standard deviation = 0.2148 (geometric standard deviation = 1.24)

11.4.3.7 Barltrop Studies. Barltrop et al. (1974) described two studies in England investigating the soil lead to blood lead relationship. In the first study, children aged 2 and 3 and their mothers from two towns chosen for their soil lead content had their blood lead levels determined from a capillary sample. Hair samples were also collected and analyzed for lead. Lead content of the suspended particulate matter and soil was measured. Soil samples for each home were a composite of several 2-inch core samples taken from the yard of each home. Chemical analysis of the lead content of soil in the two towns showed a 2- to 3-fold difference, with the values in the control town about 200-300 µg/g compared with about 700-1000 µg/g in the exposed town. A difference was also noted in the mean air lead content of the two towns, 0.60 compared with 0.29 μg/m³. Although this difference existed, both air lead values were thought low enough not to affect the blood level values differentially. Mean surface soil lead concentrations for the two communities were statistically different, the means for the high and low community being 909 and 398 μg/g, respectively. Despite this difference, no statistically significant differences in maternal blood lead levels or children's blood or hair lead levels were noted. Further statistical analysis of the data, using correlational analysis on either raw or log-transformed blood lead data, likewise failed to show a significant relationship of soil lead with either blood lead or hair lead.

The second study was reported in both preliminary and final form (Barltrop et al., 1974; Barltrop, 1975). In the more detailed report (Barltrop, 1975), children's homes were classified by their soil lead content into three groups: less than 1,000; 1,000 - 10,000; and greater than 10,000 μg/g. As shown in Table 11-60, children's mean blood lead levels increased correspondingly from 20.7 to 29.0 μg/dl. Mean soil lead levels for the low and high soil exposure groups were 420 and 13,969 μg/g, respectively. Mothers' blood levels, however, did not reflect this trend; nor were the children's fecal lead levels different across the soil exposure areas.

TABLE 11-60. MEAN BLOOD AND SOIL LEAD CONCENTRATIONS IN ENGLISH STUDY

Category of soil lead (μg/g)	Sample size	Children's blood lead (μg/dl)	Soil lead (μg/g)
<1000	29	20.7	420
1000-10000	43	23.8	3390
>10000	10	29.0	13969

Source: Barltrop, 1975.

An analysis of the data in Table 11-60 gives the following model

$$\text{blood lead } (\mu g/dl) = 0.64 \text{ soil lead } (1000\ \mu g/g) + 20.98 \qquad (11\text{-}20)$$

No confidence intervals were calculated since the calculations were based on means.

11.4.3.8 The British Columbia Studies. Neri et al. (1978) studied blood lead levels in children living in Trail, British Columbia. Capillary blood samples were collected and analyzed for lead by anodic stripping voltammetry. Duplicate samples were analyzed and the results were discarded whenever the values differed by more than 8 µg/dl. This procedure probably helped control to some degree the commonly encountered positive bias in blood lead levels observed when capillary samples are used. An episode of poisoning of horses earlier had been traced to ingestion of lead. Environmental monitoring at that time did not suggest that a human health risk existed. However, it was later thought wise to conduct a study of lead absorption in the area.

Trail had been the site of a smelter since the turn of the century. The smelter had undergone numerous changes for reasons of both health and productivity. At the time of the blood lead study, the smelter was emitting 300 pounds of lead daily, with ambient air lead levels at about 2 $\mu g/m^3$ in 1975. Nelson, BC was chosen as the control city. The cities are reasonably close (~30 miles distant), similar in population, and served by the same water basin. The average air lead level in Nelson during the study was 0.5 $\mu g/m^3$.

Initial planning called for the sampling of 200 children in each of three age groups (1-3 years, 1st grade and 9th grade) from each of the two sites. A strike at the smelter at the onset of the study caused parts of the Trail population to move. Hence, the recruited sample deviated from the planned one. School children were sampled in May, 1975 at their schools while the 1- to 3-year olds were sampled in September, 1975 at a clinic or home. This delayed sampling was intentional to allow those children to be exposed to the soil and dust for the entire summer. Blood and hair samples were collected from each child.

The children in the younger age groups living in Trail had higher blood lead levels than those living in Nelson. An examination of the frequency distributions of the blood lead levels showed that the entire frequency of the distribution shifted between the residents of the two cities. Interestingly, there was no difference in the ninth grade children.

Table 11-61 displays the results of the soil lead levels along with the blood lead levels obtained in the earlier study. Blood lead levels were higher for 1- to 3-year olds and first graders in the two nearest-to-smelter categories than in the far-from-smelter category. Again, no difference was noted for the ninth graders.

An EPA analysis of the Neri et al. (1978) data gives the following models for children 1- to 3-years old

$$\text{Blood lead } (\mu g/dl) = 0.0076 \text{ soil lead } (\mu g/g) + 15.43, \text{ and} \qquad (11\text{-}21)$$

$$\text{Blood lead } (\mu g/dl) = 0.0046 \text{ soil lead } (\mu g/g) + 16.37 \qquad (11\text{-}22)$$

for children in grade one. No confidence intervals were calculated since the analysis was based on means.

TABLE 11-61. LEAD CONCENTRATION OF SURFACE SOIL AND CHILDREN'S BLOOD BY RESIDENTIAL AREA OF TRAIL, BRITISH COLUMBIA

Residential area(s)	Mean soil lead concentration, µg/g, ± standard error (and no. of samples)	Blood lead concentration, µg/dl, mean ± standard error (and no. of children) 1- to 3-year olds	Blood lead concentration, µg/dl, mean ± standard error (and no. of children) Grade one children
1 and 2	225 ± 39 (26)	17.2 ± 1.1 (27)	18.0 ± 1.9 (18)
5	777 ± 239 (12)	19.7 ± 1.5 (11)	18.7 ± 2.3 (12)
9	570 ± 143 (11)	20.7 ± 1.6 (19)	19.7 ± 1.0 (16)
3, 4, and 8	1674 ± 183 (53)	27.7 ± 1.8 (14)	23.8 ± 1.3 (31)
6 and 7	1800 ± 212 (51)	30.2 ± 3.0 (16)	25.6 ± 1.5 (26)
Total	1320 ± 212 (153)	22.4 ± 1.0 (87)	21.9 ± 0.7 (103)

Source: Schmitt et al., 1979.

11.4.3.9 The Baltimore Charney Study: A Controlled Trial of Household Dust Lead Reduction. Charney et al. (1983) selected children from the Lead Poisoning Clinic of the John F. Kennedy Institute in Baltimore. The children were all 15-72 months old at the time of enrollment and had at least two venous blood lead levels between 30 and 49 µg/dl and FEP < 655 µg/dl. The children were also required to have had the same place of residence for at least the preceding six months. Their houses had to have been deleaded in accordance with standard procedures used by the Baltimore City Health Department. Experimental control subjects were recruited on the basis of attendance at routine periodic blood lead monitoring. Alternative identification numbers were used for allocation to experimental and control groups. Home visits were made for children in the experimental group and a 930 cm^2 area of the floor or windowsill was wiped with an alcohol-treated cloth towel and the dust lead content analyzed. A "dust control team" then visited each home twice monthly and wet-mopped all surfaces with >100 µg Pb per 930 cm^2. The child's caretaker was advised to wet-mop these surfaces and other "hot spots" more frequently, to wash the child's hands before meals and at bedtime, and to restrict access to high-lead areas.

Both the 14 experimental subjects receiving the above treatment and the 35 control subjects started the study with about the same moderately elevated blood lead levels, 38.6 ± 5.2 µg/dl at the start of the experiment. These levels had remained almost stationary for six months before the experiment, increasing only 1 µg/dl on average. After a year of dust control, the experimental subjects had reduced their PbB levels by 6.9 µg/dl, whereas the control subjects had reduced their PbB levels insignificantly (0.7 µg/dl). Five of the control subjects actually had increased PbB by 6-12 µg/dl, and one by 20 µg/dl. None of the dust-controlled subjects had any PbB increase, and most showed a decrease of at least 6 µg/dl. Four experimental subjects had PbB < 30 µg/dl by the end of the experiment.

Dust lead levels in experimentally cleaned homes returned to nearly the previous high values within two weeks. There was no significant relation between reduction of leaded dust, initial level of leaded dust, and the reduction in a child's blood lead level. This lack of apparent correlation may have been due to failure to control or monitor hand washing, finger-sucking and mouthing behavior, access to "hot spots," and time spent in the home. Furthermore, attempts at dust control may have been more successful in some of the control homes than in others, resulting in blood lead reduction in at least some individual cases. Since advice on dust control was offered to caretakers of lead-burdened children visiting the Clinic, it may be presumed that some measure of dust control would have occurred in any event. Dust lead values in the experimental homes were high compared to homes in other areas (13/14 had sites >100 µg/930 cm^2). While many potentially important factors were not completely controlled during the trials, the importance of dust ingestion is evident. This study also points out the difficulties in quantifying the dust-hand-mouth pathway using familiar measures of household dust lead and concentration. Since the reduction in blood lead levels cannot be plausibly attributed to factors other than household dust control (e.g., relocation of residence or change in diet), the experimental evidence for the importance of household dust in elevation of blood lead levels in U.S. urban children is very strong.

11.4.3.10 Gallacher Study. A report from England (Gallacher et al., 1984) provides additional informative data on the importance of dust to blood lead levels. They were interested in the effect of pica on blood lead levels. Mothers and children aged 1-3 years were recruited from 4 areas of Wales chosen for presumed lead exposure: 1) roadside dwellings; 2) cul de sac dwellings; 3) an old mining area; and 4) a control area. Comprehensive environmental sampling accompanied the study of blood lead levels. Indoor air samples, soil from play areas, pavement dust, house dust, and tap water samples were collected and analyzed for lead content. Capillary blood samples were collected from the children, while venous samples were collected from the mothers. Blood samples were analyzed for lead by atomic absorption spectrophotometry. The accuracy of the capillary sampling was checked; the authors concluded that contamination was not a problem but that the values of the capillary samples were 37 percent higher than venous samples. They attributed the difference as "probably owing to haemoconcentration of capillary blood."

Results from the environmental sampling indicated that for many of the environmental media, lead exposures were reasonably constant over a several-month period. The authors state that, "Coefficient of variation..., based on duplicate pairs and after logarithmic transformation, was 9 percent for pavement dwellings (22 dwellings) and 10 percent for housedust (25 dwellings). The coefficient of variation of child hand lead using the 'wet wipe' technique was 19 percent (based on 17 children)." The coefficient of variation of the blood lead sample of venous blood was around 7 percent.

In both children and mothers, the mining area differed the most from the control area. The excess of lead in the blood of children was 30 percent for the mining area; in mothers the excess was about 50 percent.

Pica as determined by questionnaire showed no consistent association with any area or all areas combined. On the other hand, the analysis of the wet wipe study provided interesting results. Within the roadside dwellings, the cul de sacs, and the control areas, mean lead levels of wet wipe samples were remarkably similar for mothers' hands, children's hands, and kitchen surfaces. But the mining area had a 40 percent excess for mothers' hands, 45 percent for children's hands, and 35 percent for kitchen surfaces, compared to the control area. However, the only difference which was statistically significant was for the children.

Correlation analysis was performed between blood lead concentrations and hand lead concentrations. In the mining area, which was the most contaminated area, the correlation coefficient was 0.38, which was statistically significantly different from zero. In the noncontaminated areas, a statistically significant relationship was found between blood lead and kitchen surface. No statistically significant relations were seen for the mothers. Thus these data give additional support to the notion of normal hand-to-mouth activity being a pathway by which lead in dust can get into the blood of children.

11.4.3.11 Other Studies of Soil and Dusts. Rabinowitz et al. (1985c) report in a study discussed in Section 11.3.5.4 that lead levels in indoor dust and outdoor soil were strongly predictive of blood lead levels. Their sample consisted of Boston urban and suburban infants followed from birth to 2 years of age whose mothers had a mean age of 29 years and 15 years mean schooling.

Lepow et al. (1975) studied the lead content of air, house dust, and dirt, as well as the lead content of dirt on hands, food and water, to determine the cause of chronically elevated blood lead levels in 10 children 2 to 6 years old in Hartford, Connecticut. Lead-based paints had been eliminated as a significant source of lead for these children. Ambient air lead concentrations varied from 1.7 to 7.0 µg/m^3. The mean lead concentration in dirt was 1,200 µg/g and in dust, 11,000 µg/g. The mean concentration of lead in dirt on children's hands was 2,400 µg/g. The mean weight of samples of dirt from hands was 11 mg, which represented only a small fraction of the total dirt on hands. Observation of the mouthing behavior in these young children led to the conclusion that the hands-in-mouth exposure route was the principal cause of excessive lead accumulation.

Several studies have investigated the mechanism by which lead from soil and dust gets into the body (Sayre et al., 1974; Ter Haar and Aronow, 1974). Sayre et al. (1974) in Rochester, New York, demonstrated the feasibility of house dust as a source of lead for children. Two groups of houses, one inner city and the other suburban, were chosen for the study. Lead-free sanitary paper towels were used to collect dust samples from house surfaces and the hands of children (Vostal et al., 1974). The medians for the hand and household samples were used as the cutpoints in the chi-square contingency analysis. A statistically significant difference between the urban and suburban homes for dust levels was noted, as was a relationship between household dust levels and hand dust levels (Lepow et al., 1975).

Ter Haar and Aronow (1974) investigated lead absorption in children that can be attributed to ingestion of dust and dirt. They reasoned that because the proportion of the naturally occurring isotope of ^{210}Pb varies for paint chips, airborne particulates, fallout dust, house dust, yard dirt, and street dirt, it would be possible to identify the sources of ingested lead. They collected 24-hour excreta from eight hospitalized children on the first day of hospitalization. These children, 1 to 3 years old, were suspected of having elevated body burdens of lead, and one criterion for the suspicion was a history of pica. Ten children of the same age level, who lived in good housing in Detroit and the suburbs, were selected as controls and 24-hour excreta were collected from them. The excreta were dried and stable lead as well as ^{210}Pb content determined. For seven hospitalized children, the stable lead mean value was 22.43 μg/g dry excreta, and the eighth child had a value of 1640 μg/g. The controls' mean for stable lead was 4.1 μg/g dry excreta. However, the respective means for ^{210}Pb expressed as pCi/g dry matter were 0.044 and 0.040. The authors concluded that because there is no significant difference between these means for ^{210}Pb, the hypothesis that young children with pica eat dust is not supported. The authors further concluded that children with evidence of high lead intake did not have dust and air suspended particulate as the sources of their lead. It is clear that air suspended particulate did not account for the lead levels in the hospitalized children. However, the ^{210}Pb concentrations in dust and feces were similar for all children, making it difficult to estimate the dust contribution.

Heyworth et al. (1981) studied a population of children exposed to lead in mine tailings. These tailings were used in foundations and playgrounds, and had a lead content ranging from 10,000 to 15,000 μg/g. In December, 1979, venous blood samples and hair were collected from 181 of 346 children attending two schools in Western Australia. One of the schools was a primary school; the other was a combined primary and secondary school. Parents completed questionnaires covering background information as well as information regarding the children's exposure to the tailings. Blood lead levels were determined by the AAS method of Farrely and Pybos. Good quality control measures were undertaken for the study, especially for the blood lead levels. Blood lead levels were higher in boys versus girls (mean values were 14.0 and 10.4 µg/dl, respectively). This difference was statistically significant. Five percent of the children (n = 9) had blood lead levels greater than 25 µg/dl; five of these children had blood lead levels greater than 30 µg/dl. Blood lead levels decreased significantly with age and were slightly lower in children living on properties on which tailings were used. However, they were higher for children attending the school that used the tailings in the playground.

Landrigan et al. (1982) studied the impact on soil and dust lead levels on removal of leaded paint from the Mystic River Bridge in Masschusetts. Environmental studies in 1977 indicated that surface soil directly beneath the bridge had a lead content ranging from 1300 to 1800 µg/g. Analysis of concomitant trace elements showed that the lead came from the bridge. A concurrent survey of children living in Chelsea (vicinity of bridge) found that 49 percent of 109 children had blood lead levels greater than or equal to 30 µg/dl. Of children living more distant from the bridge, 37 percent had that level of blood lead.

These findings prompted the Massachusetts Port Authority to undertake a program to delead the bridge. Paint on parts of the bridge that extended over neighborhoods was removed by abrasive blasting and replaced by zinc primer. Some care was undertaken to minimize both the occupational as well as environmental exposures to lead as a result of the blasting process.

Concurrently with the actual deleading work, a program of air monitoring was established to check on the environmental lead exposures being created. In June, 1980, four air samples taken at a point 27 m from the bridge had a mean lead content of 5.32 µg/m^3. As a result of these findings air pollution controls were tightened; mean air lead concentrations 12 meters from the bridge in July were 1.43 µg/m^3.

Samples of the top 1 cm of soil were obtained in July, 1980 from within 30, 30-80, and 100 m from the bridge. Comparison samples from outside the area were also obtained. Samples taken directly under the bridge had a mean lead content of 8127 µg/g. Within 30 m of the bridge, the mean content was 3272 µg/g, dropping to 457 µg/g at 30 to 80 m. At 100 m the soil lead level dropped to 197 µg/g. Comparison samples ranged from 83 to 165 µg/g depending on location.

Fingerstick blood samples were obtained on 123 children 1-5 years of age living within 0.3 km of the bridge in Charlestown. Four children (3.3 percent) had blood lead levels greater than 30 µg/dl, with a maximum of 35 µg/dl. All four children lived within two blocks of the bridge. Two of the four had lead paint in their homes but it was intact. None of the 76 children living more than two blocks from the bridge had blood leads greater than or equal to 30 µg/dl, a statistically significant difference.

Shellshear's (1973) case report from New Zealand ascribes a medically diagnosed case of lead poisoning to high soil lead content in the child's home environment. Shellshear et al.

(1975) followed up his case report of increased lead absorption resulting from exposure to lead contaminated soil with a study carried out in Christchurch, New Zealand. Two related activities comprised the study. First, from May, 1973 to November, 1973, a random study of pediatric admissions to a local hospital was made. Blood samples were taken and analyzed for lead. Homes were visited and soil samples were collected and analyzed for lead. Lead analyses for both soil and blood were conducted by AAS. Second, a soil survey of the area was undertaken. Whenever a soil lead value greater than 300 µg/g was found and a child aged 1-5 was present, the child was referred for blood testing.

The two methods of subject recruitment yielded a total of 170 subjects. Eight (4.7 percent) of the children had blood lead equal to or greater than 40 µg/dl, and three of them had a blood lead equal to or greater than 80 µg/dl. No correlation with age was noted. The mean blood lead of the pediatric admissions was 17.5 µg/dl with an extremely large range (4-170 µg/dl). The mean blood lead for soil survey children was 19.5 µg/dl.

Christchurch was divided into two sections based on the date of development of the area. The inner area had developed earlier and a higher level of lead was used there in the house paints. The frequency distribution of soil lead levels showed that the inner zone samples had much higher soil lead levels than the outer zone. Furthermore, analysis of the soil lead levels by type of exterior surface of the residential unit showed that painted exteriors had higher soil lead values than brick, stone, or concrete block exteriors.

Analysis of the relationship between soil lead and blood lead was restricted to children from the sampled hospital who had lived at their current address for at least one year. Table 11-62 presents the analysis of these results. Although the results were not statistically significant, they are suggestive of an association.

TABLE 11-62. ANALYSIS OF RELATIONSHIP BETWEEN SOIL LEAD AND BLOOD LEAD IN CHILDREN

	Soil lead (µg/g)			Blood lead (µg/dl)	
Area of city	Mean	Range	n	Mean	Range
Inner zone	1950	30-11000	21	25.4	4-170
Outer zone	150	30-1100	47	18.3	5-84

Source: Shellshear (1973).

Analysis of the possible effect of pica on blood lead levels showed the mean blood lead for children with pica to be 32 µg/dl while those without pica had a mean of 16.8 µg/dl. The pica blood lead mean was statistically significantly higher than the non-pica mean.

Mielke et al. (1984) reports elevated blood lead and FEP levels among Hmong children living in Minneapolis, Minnesota. The lead sources for these children included soil lead, house paint, and leaded gasoline from vehicle traffic. Fifty percent of children with lead poisoning (FEP > 50 µg/dl, blood lead > 30 µg/dl) inhabited homes which had soil lead levels of 500 to 1000 µg/g.

Wedeen et al. (1978) reported a case of lead nephropathy in a black female who exhibited geophagia. The patient, who had undergone chelation therapy, eventually reported that she had a habit of eating soil from her garden in East Orange, New Jersey. During spring and summer, she continuously kept soil from her garden in her mouth while gardening. She even put a supply away for winter. The soil was analyzed for lead and was found to contain almost 700 µg/g. The authors estimated that the patient consumed 100-500 mg of lead each year. One month after initial hospitalization her blood lead level was 70 µg/dl.

11.4.3.12 Summary of Soil and Dust Lead. Studies relating soil lead to blood lead levels are difficult to compare. The relationship obviously depends on depth of soil lead, age of the children, sampling method, cleanliness of the home, mouthing activities of the children, and possibly many other factors. Brunekreef et al. (1983) studied a population of urban and rural children in the Netherlands. The analyses are described in detail in Section 11.4.3.4. Blood lead levels increased with increasing outside dustfall, with increased lead on children's hands, and with pets in the household, and decreased with increasing number of rooms (due to dilution or confounded SES effects). Dust lead and its related transport factors substantially increased blood lead. Table 11-63 gives some estimated slopes taken from several different studies. The range of these values is quite large, ranging from 0.6 to 6.8. This range is similar to the range of 1.0 to 10.0 reported by Duggan (1980, 1983). Two studies providing good data for slope estimates are the Stark et al. (1982) study and the Angle and McIntire (1982) study. These two studies gave slope estimates of 2.2 and 6.8 µg/dl per 1000 µg/g, respectively.

The relationship of house dust lead to blood lead is even more difficult to obtain. Table 11-64 contains some values for three studies that give data permitting such caculations. The median value of 1.8 µg/dl per 1000 µg/g for children 2-3 years old in the Stark study may also represent a reasonable value for use here.

11.4.4 Paint Lead Exposures

A major source of environmental lead exposure for some in the general population comes from lead contained in both interior and exterior paint on dwellings. The amount of lead present, as well as its accessibility, depends upon the age of the residence (because older

TABLE 11-63. ESTIMATES OF THE CONTRIBUTION OF SOIL LEAD TO BLOOD LEAD

Study	Range of soil lead values (μg/g)	Depth of sample	Estimated slope (X10^3)	Sample size	R^2
Angle and McIntire (1982) study of children in Omaha, NE	16-4792	2"	6.8	1075	0.198
Stark et al. (1982) study of children in New Haven, CT	30 - 7000 (age 0-1)	½"	2.2	153	0.289
	30 - 7600 (age 2-3)		2.0	334	0.300
Yankel et al. (1977) study of children in Kellogg, ID	50 - 24,600	3/4"	1.1	860	0.662
Galke et al. (1975) study of children in Charleston, SC	9 - 7890	2"	1.5	194	0.386
Barltrop et al. (1975) study of children in England	420 - 13,969 (group means)	2"	0.6	82	NA*
Neri et al. (1978) study of children in British Columbia	225-1800 (group means, age 1-3)	NA	7.6	87	NA
	225-1800 (group means, age 2-3)	NA	4.6	103	NA

*NA means Not Available.

TABLE 11-64. ESTIMATES OF THE CONTRIBUTION OF HOUSEDUST TO BLOOD LEAD IN CHILDREN

Study	Range of dust lead values (μg/g)	Age range in years	Estimated slope ($X10^3$)	Sample size	R^2
Angle and McIntire (1979) study in Omaha, NE	18-5571	1-18	7.18	1074	0.198
		6-18	3.36	832	0.262
Stark et al. (1982) study in New Haven, CT	70-7600	0-1	4.02	153	0.289
	40-7600	2-3	1.82	334	0.300
	9-4900	4-7	0.02	439	0.143
Yankel et al. (1977) study in Kellogg, ID	50-35,600	0-4	0.19	185	0.721
		5-9	0.20	246	0.623

buildings contain paint manufactured before lead content was regulated) and the physical condition of the paint. It is generally accepted by the public and by health professionals that lead-based paint is one major source of overtly symptomatic pediatric lead poisoning in the United States (Lin-Fu, 1973).

The level and distribution of lead paint in a dwelling is a complex function of history, geography, economics, and the decorating habits of its residents. Lead pigments were the first pigments produced on a large commercial scale when the paint industry began its growth in the early 1900's. In the 1930's lead pigments were gradually replaced with zinc and other opacifiers. By the 1940's, titanium dioxide became available and is now the most commonly used pigment for residential coatings. There was no regulation of the use of lead in house paints until 1955, when the paint industry adopted a voluntary standard that limited the lead content in interior paint to no more than 1 percent by weight of the nonvolatile solids. At about the same time, local jurisdictions began adopting codes and regulations that prohibited the sale and use of interior paints containing more than 1 percent lead (Berger, 1973a,b).

In spite of the change in paint technology and local regulations governing its use, interior paint with significant amounts of lead was still available in the 1970's. Studies by Berger (1973b) and by the U.S. Consumer Product Safety Commission (1974) showed a continuing decrease in the number of interior paints with lead levels greater than 1 percent. By 1974, only 2 percent of the interior paints sampled were found to have greater than 1 percent lead in the dried film (U.S. Consumer Product Safety Commission, 1974).

The level of lead in paint in a residence that should be considered hazardous remains in question. Not only is the total amount of lead in paint important, but also the accessibility of the painted surface to a child, as well as the frequency of ingestion, must be considered. Attempts to set an acceptable lead level, in situ, have been unsuccessful, and preventive control measures of lead paint hazards have been concerned with lead levels in currently manufactured paint. In one of its reviews, the NAS concluded: "Since control of the lead paint hazard is difficult to accomplish once multiple layers have been applied in homes over two to three decades, and since control is more easily regulated at the time of manufacture, we recommend that the lead content of paints be set and enforced at time of manufacture" (National Academy of Sciences, 1976).

Legal control of lead paint hazards is being attempted by local communities through health or housing codes and regulations. At the Federal level, the Department of Housing and Urban Development has issued regulations for lead hazard abatement in housing units assisted or supported by its programs. Generally, the lead level considered hazardous ranges from 0.5 to 2.5 mg/cm^2, but the level of lead content selected appears to depend more on the sensitivity of field measurement (using X-ray fluorescent lead detectors) than on direct biological dose-response relationships. Regulations also require lead hazard abatement when the paint is loose, flaking, peeling, or broken, or in some cases when it is on surfaces within reach of a child's mouth.

Some studies have been carried out to determine the distribution of lead levels in paint in residences. A survey of lead levels in 2370 randomly selected dwellings in Pittsburgh provides some indication of the lead levels to be found (Shier and Hall, 1977). Figure 11-29 shows the distribution curves for the highest lead level found in dwellings for three age groupings. The curves bear out the statement often made that paint with high levels of lead is most frequently found in pre-1940 residences. One cannot assume, however, that high lead paint is absent in dwellings built after 1940. In the case of the houses surveyed in Pittsburgh, about 20 percent of the residences built after 1960 have at least one surface with more than 1.5 mg/cm^2.

The distribution of lead within an individual dwelling varies considerably. Lead paint is most frequently found on doors and windows where lead levels greater than 1.5 mg/cm^2 were found on 2 percent of the surfaces surveyed, whereas only about 1 percent of the walls had lead levels greater than 1.5 mg/cm^2 (Shier and Hall, 1977).

In a review of the literature, Lin-Fu (1973) found general acceptance that the presence of lead in paint is necessary but not sufficient evidence of a hazard. Accessibility in terms of peeling, flaking, or loose paint also provide evidence for the presence of a hazard. Of the total samples surveyed, about 14 percent of the residences had accessible paint with a lead content greater than 1.5 mg/cm^2. As discussed in Section 7.3.2.1.2, one must note that lead oxides of painted surfaces contribute to the lead level of house dust.

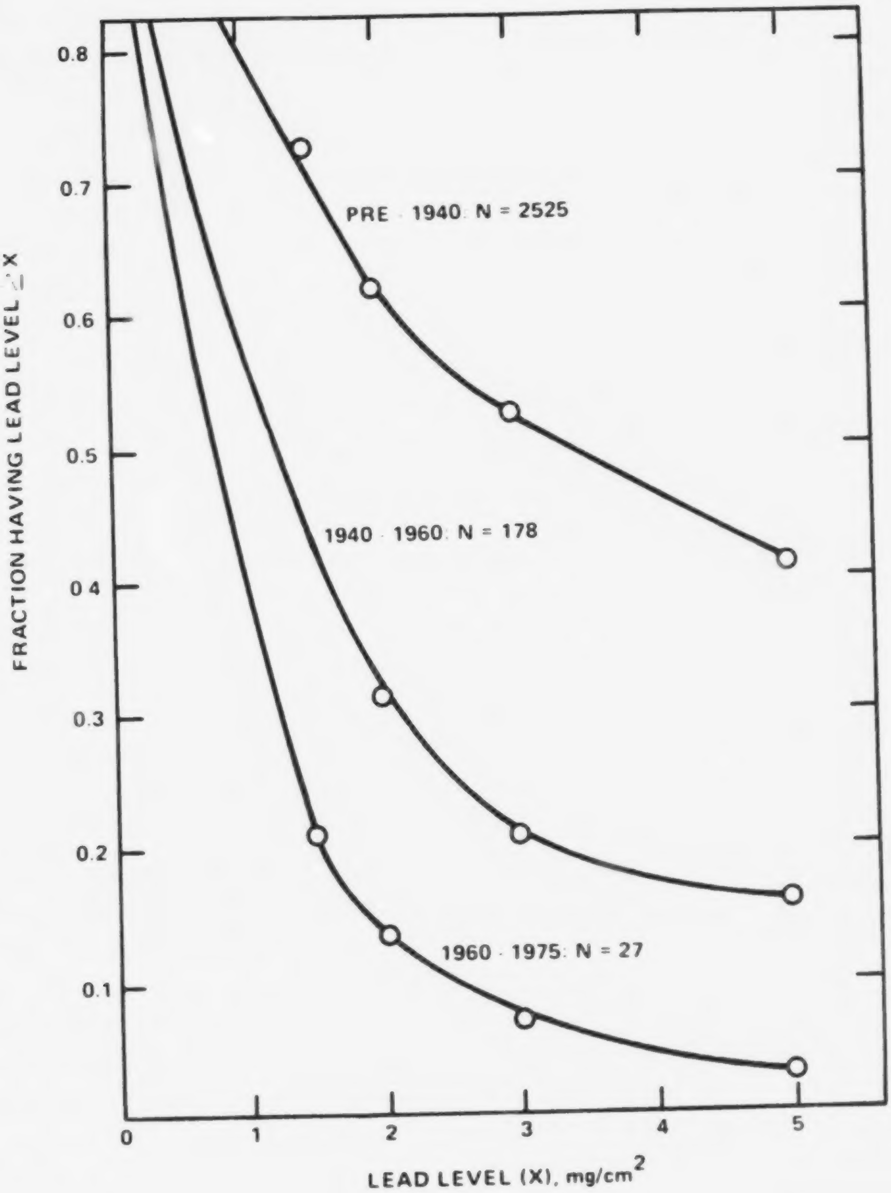

Figure 11-29. Cumulative distribution of lead levels in dwelling units.

Source: Shier and Hall (1977).

It is not possible to extrapolate the results of the Pittsburgh survey nationally. However, additional data from a pilot study of 115 residences in Washington, DC, showed similar results (Hall 1974).

An attempt was made in the Pittsburgh study to obtain information about the correlation between the quantity and condition of lead paint in buildings, and the blood lead of children who resided there (Urban, 1976). Blood lead analyses and socioeconomic data for 456 children were obtained, along with the information about lead levels in the dwelling. Figure 11-30 is a plot of the blood lead levels versus the fraction of surfaces within a dwelling with lead levels of at least 2 mg/cm^2. Analysis of the data shows a low correlation between the blood lead levels of the children and fraction of surfaces with lead levels above 2 mg/cm^2, but there is a stronger correlation between the blood lead levels and the condition of the painted surfaces in the dwellings in which children reside. This latter correlation appeared to be independent of the lead levels in the dwellings.

Yaffe et al. (1983) report data that suggests that soil lead possibly derived from exterior paint was an important source for a selected group of children. They used a stable lead isotope ratio technique.

Hammond et al. (1981, 1982) conducted a study of Cincinnati children with the dual purpose of determining whether inner city children with elevated blood lead levels have elevated fecal lead and whether fecal lead correlates with lead-base paint hazard in the home or traffic density as compared with blood lead. Subjects with high blood lead levels were primarily recruited. Some comparison children with low blood lead levels were also identified. The three comparison children had to be residentially stable so that their low blood lead levels were reflective of the lead intake of their current environment. The subjects from the inner city were usually from families in extremely depressed socio-economic circumstances. Stool samples were collected on a daily basis for up to 3 weeks, then analyzed for lead. Fecal lead levels were expressed both as mg/kg·day and as mg/m^2·day.

An environmental assessment was made at the home of each child. Paint lead exposure was rated on a three-point scale (high, medium, and low) based on paint lead level and integrity of the painted wall. Air lead exposure was assessed by the point scale (high, medium, and low) based on traffic density, because there are no major point sources of lead in the Cincinnati area.

Blood samples were collected on an irregular basis but were taken sufficiently often to have at least one sample from a child from every house studied. The blood samples were analyzed for lead by two laboratories that had different histories of performance in the CDC proficiency testing program. All blood lead levels used in the statistical analysis were adjusted to a common base. Because of the variable number of fecal and blood lead levels, the data were analyzed using a nested analysis of variance.

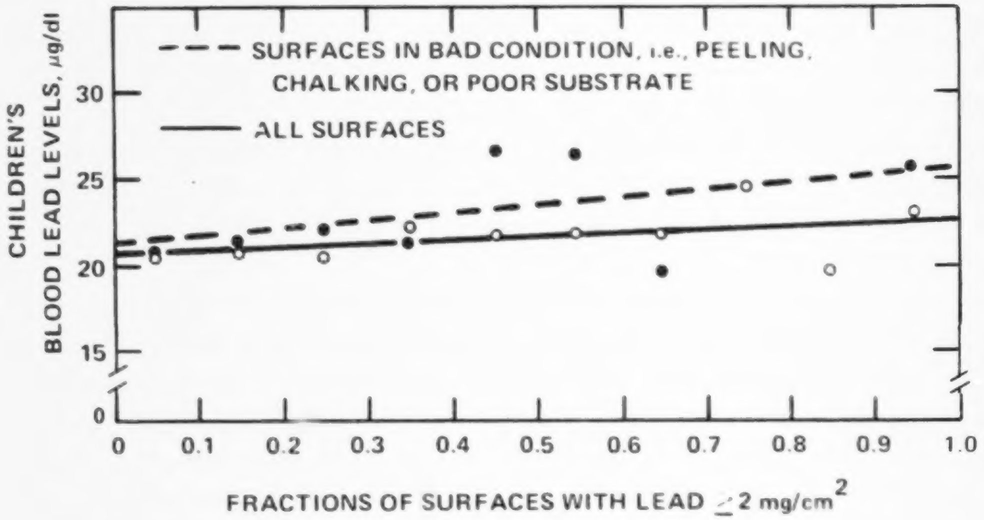

Figure 11-30. Correlation of children's blood lead levels with fractions of surfaces within a dwelling having lead concentrations ≥ 2 mg Pb/cm².

Source: Urban (1976).

The homes of the children were found to be distributed across the paint and traffic lead exposure categories. Both fecal lead levels and blood levels were positively associated with interior paint lead hazard. A marginal association between fecal lead levels and exterior paint hazard was also obtained. Neither fecal lead nor blood lead was found to be associated with traffic density; the definition of the high traffic density category, however, began at a low level of traffic flow (7500 cars/day).

Examination of fecal and blood lead levels by sex and race showed that black males had the highest fecal lead excretion rates followed by white males and black females. White females were only represented by two subjects, both of whom had high fecal lead excretion. Blood lead levels were more influenced by race than by sex. The results suggested that children in high and medium paint hazard homes (high = at least 1 surface with >0.5 percent Pb, peeling or loose) were probably ingesting paint in some form. This could not be confirmed, however, by finding physical evidence in the stools.

Long-term stool collection in a subset of 13 children allowed a more detailed examination of the pattern of fecal lead excretion. Two patterns of elevated fecal lead excretion were noted. The first was a persistent elevation compared with controls; the second was markedly elevated occasional spikes against a normal background.

One family moved from a high-hazard home to a low one during the course of the study. This allowed a detailed examination of the speed of deleading of fecal and blood lead level. The fecal levels decreased faster than the blood lead levels. The blood leads were still elevated at the end of the collection.

Gilbert et al. (1979) studied a population of Hispanic youngsters in Springfield, Massachusetts, in a case control study designed to compare the presence of sources of lead in homes of lead-poisoned children and appropriately matched controls. Cases were defined as children having two consecutive blood lead levels greater than 50 µg/dl. Controls were children with blood lead levels less than or equal to 30 µg/dl who had no previous history of lead intoxication and were not siblings of children with blood lead levels greater than 30 µg/dl. Study participants had to be residentially stable for at least 9 months and not have moved into their current home from a lead contaminated one. All blood lead levels were analyzed by Delves cup method of AAS. Cases and controls were matched by age (±3 months), sex, and neighborhood area. The study population consisted of 30 lead intoxication cases and 30 control subjects.

Home visits were undertaken to gather interview information and conduct home inspection. Painted surfaces were assessed for integrity of the surface and lead content. Lead content was measured by X-ray fluorometry. A surface was scored as positive if the lead content exceeded 1.2 mg/cm^2. Drinking water lead was assessed for each of the cases and was found to contain less than 50 μg/l, thought by the authors to be sufficiently low so as not to constitute a hazard. Tap water samples were not collected in the homes of the controls. Soil samples were collected from three sites in the yard and analyzed for lead by X-ray fluorometry.

Cases and controls were compared on environmental lead exposures and interview data using McNemar's test for paired samples. The odds ratio was calculated as an estimator of the relative risk on all comparisons. Statistically significant differences between cases and controls were noted for lead in paint and the presence of loose paint. Large odds ratios (>10) were obtained, suggesting a very strong association of blood lead level and paint lead exposure. There appeared to be little influence of age or sex on the odds ratios.

Significant differences between cases and controls were obtained for both intact and loose paint by individual surfaces within specific living areas of the home. Surfaces accessible to children were significantly associated with lead poisoning status while inaccessible surfaces generally were not. Interestingly, the odds ratios tended to be larger for the intact surface analysis than for the loose paint one.

Median paint lead levels in the homes of cases were substantially higher than those in the homes of controls. The median paint lead for exterior surfaces in cases was about 16-20 $\mu g/cm^2$ and about 10 $\mu g/cm^2$ for interior surfaces. Control subjects lived in houses in which the paint lead generally was less than 1.2 $\mu g/cm^2$ except for some exterior surfaces. Soil lead was significantly associated with lead poisoning; the median soil lead level for homes of cases was 1430 μg/g, while the median soil lead level for control homes was 440 μg/g.

Rabinowitz et al. (1985b) report that refinishing activity in homes with high paint lead was associated with elevations of blood lead averaging 69 percent. Blood lead levels of 249 infants were measured semiannually from birth to two years of age. Also, home paint was sampled and any recent home refinishing was recorded. Mean blood lead correlated significantly with the amount of lead in the indoor paint.

Two other studies have attempted to relate blood lead levels and paint lead as determined by X-ray fluorescence. Reece et al. (1972) studied 81 children from two lower socioeconomic communities in Cincinnati. Blood leads were analyzed by the dithizone method. There was considerable lead in the home environment, but it was not reflected in the children's blood lead. Analytical procedures used to test the hypothesis were not described; neither were the raw data presented.

Galke et al. (1975), in their study of inner-city black children, measured the paint lead, both interior and exterior, as well as soil and traffic exposure. In a multiple regression analysis, exterior siding paint lead was found to be significantly related to blood lead levels.

Evidence indicates that a source of exposure in childhood lead poisoning is peeling lead paint and broken lead-impregnated plaster found in poorly maintained houses. There are also reports of exposure cases that cannot be equated with the presence of lead paint. Further, the analysis of paint in homes of children with lead poisoning has not consistently revealed a hazardous lead content (Lin-Fu, 1973). For example, one paper reported 5466 samples of paint obtained from the home environment of lead poisoning cases in Philadelphia between 1964 and 1968. Among these samples of paint, 67 percent yielded positive findings, i.e., paint with more than 1 percent lead (Tyler, 1970).

Data published or made available by the Centers for Disease Control also show that a significant number of children with undue lead absorption occupy buildings that were inspected for lead-based paint hazards, but in which no hazard could be demonstrated (U.S. Centers for Disease Control, 1977a; Hopkins and Houk, 1976). Table 11-65 summarizes the data obtained from the HEW-funded lead-based paint poisoning control projects for Fiscal Years 1981, 1979, 1978, 1975, and 1974. These data show that in Fiscal Years 1974, 1975, and 1978, in 40-50 percent of confirmed cases of elevated blood lead levels, a possible source of lead paint hazard was not located. In fiscal year 1981, the U.S. Centers for Disease Control (1982a,b), screened 535,730 children and found 21,897 with lead toxicity. Of these, 15,472 dwellings were inspected and 10,666 or approximately 67 percent were found to have leaded paint. The implications of these findings are not clear. The findings are presented in order to place in proper perspective both the concept of total lead exposure and the concept that lead paint is one source of lead that contributes to the total body load. The background contribution of lead from other sources is still not known, even for those children for whom a potential lead paint hazard has been identified; nor is it known what proportion of lead came from which source.

TABLE 11-65. RESULTS OF SCREENING AND HOUSING INSPECTION IN CHILDHOOD LEAD POISONING CONTROL PROJECT BY FISCAL YEAR

Results	Fiscal year				
	1981	1979	1978	1975	1974
Children screened	535,730	464,751	397,963	440,650	371,955
Children with elevated lead exposure	21,897	32,537	25,801	28,597[a]	16,228[a]
Dwellings inspected	15,472	17,911	36,138	30,227	23,096
Dwellings with lead hazard	10,666	12,461	18,536	17,609	13,742

[a] Confirmed blood lead level $\geq$40 µg/dl.

Source: U.S. Centers for Disease Control (1977a, 1979, 1980, 1982a,b); Hopkins and Houk, 1976.

11.5 SPECIFIC SOURCE STUDIES

The studies reviewed in this section all provide important information regarding specific environmental sources of airborne lead that play a role in population blood lead levels. These studies also illustrate several interesting approaches to this subject.

11.5.1 Primary Smelter Populations

Some studies of nonindustry-employed populations living in the vicinity of industrial sources of lead pollution were triggered because evidence of severe health impairment had been found. Subsequently, extremely high exposures and high blood lead concentrations were found. The following studies document the excessive lead exposure that developed, as well as some of the relationships between environmental exposure and human response.

11.5.1.1 El Paso, Texas. In 1972, the Centers for Disease Control studied the relationships between blood lead levels and environmental factors in the vicinity of a primary smelter located in El Paso, Texas emitting lead, copper, and zinc. The smelter had been in operation since the late 1800's (Landrigan et al., 1975; U.S. Centers for Disease Control, 1973). Daily hi-vol samples collected on 86 days between February and June, 1972, averaged 6.6 µg/m^3. These air lead levels fell off rapidly with distance, reaching background values approximately 5 km from the smelter. Levels were higher downwind, however. High concentrations of lead in soil and house dusts were found, with the highest levels occurring near the smelter. The geometric means of 82 soil and 106 dust samples from the sector closest to the smelter were 1791 and 4022 µg/g, respectively. Geometric means of both soil and dust lead levels near the smelter were significantly higher than those in study sectors 2 or 3 km farther away.

Sixty-nine percent of children 1 to 4 years old living near the smelter had blood lead levels greater than 40 µg/dl, and 14 percent had blood lead levels that exceeded 60 µg/dl. Concentrations in older individuals were lower; nevertheless, 45 percent of the children 5 to 9 years old, 31 percent of the individuals 10 to 19 years old, and 16 percent of the individuals above 19 had blood lead levels exceeding 40 µg/dl. The data presented preclude calculations of means and standard deviations.

Data for people aged 1-19 years of age living near the smelter showed a relationship between blood lead levels and concentrations of lead in soil and dust. For individuals with blood lead levels greater than 40 µg/dl, the geometric mean concentration of lead in soil at their homes was 2587 µg/g, whereas for those with a blood lead concentration less than 40 µg/dl, home soils had a geometric mean of 1419 µg/g. For house dust, the respective geometric means were 6447 and 2067 µg/g. Length of residence was important only in the sector nearest the smelter.

Additional sources of lead were also investigated. A relationship was found between blood lead concentrations and lead release from pottery, but the number of individuals exposed to lead-glazed pottery was very small. No relationships were found between blood lead levels and hours spent out-of-doors each day, school attendance, or employment of a parent at the smelter. The reported prevalence of pica also was minimal.

Data on dietary intake of lead were not obtained because there was no food available from sources near the smelter since the climate and proximity to the smelter prevented any farming in the area. It was unlikely that the dietary lead intakes of the children from near the smelter or farther away were significantly different. It was concluded that the primary factor associated with elevated blood lead levels in the children was ingestion or inhalation of dust containing lead.

Morse et al. (1979) conducted a follow-up investigation of the El Paso smelter to determine whether the environmental controls instituted following the 1972 study had reduced the lead problem described. In November, 1977, all children 1 to 18 years old living within 1.6 km of the smelter on the U.S. side of the border were surveyed. Questionnaires were administered to the parents of each participant to gather background data.

Venous blood samples were drawn and analyzed for lead by modified Delves cup spectrophotometry. House dust and surface soil samples, as well as sample pottery items, were taken from each participant's residence. Dust and soil samples were analyzed for lead by AAS. Pottery lead determinations were made by the extraction technique of Klein. Paint, food, and water specimens were not collected because the earlier investigations of the problem had demonstrated these media contributed little to the lead problem in El Paso.

Fifty-five of 67 families with children (82 percent) agreed to participate in the study. There were 142 children examined in these homes. The homes were then divided into two groups. Three children lived in homes within 0.8 km of the smelter. Their mean blood lead level in 1977 was 17.7 µg/dl. By contrast, the mean blood lead level of 160 children who lived within 0.8 km of the smelter in 1972 had been 41.4 µg/dl. In 1977, 137 children lived in homes located 0.8-1.6 km from the smelter. Their mean blood lead level was 20.2 µg/dl. The mean blood level of 96 children who lived in that same area in 1972 had been 31.2 µg/dl.

Environmental samples showed a similar improvement. Dust lead fell from 22,191 to 1,479 µg/g while soil lead fell from 1,791 to 427 µg/g closest to the smelter. The mean air lead concentration at 0.4 km from the smelter decreased from 10.0 to 5.5 µg/m^3 and at 4.0 km from 2.1 to 1.7 µg/m^3. Pottery was not found to be a problem.

11.5.1.2 CDC-EPA Study. Baker et al. (1977b), in 1975, surveyed 1774 children 1-5 years old, most of whom lived within 4 miles of lead, copper, or zinc smelters located in various parts of the United States. Blood lead levels were modestly elevated near 2 of the 11 copper and 2 of the 5 zinc smelters. Although blood lead levels in children were not elevated in the vicinity of three lead smelters, their FEP levels were somewhat higher than those found in controls. Increased levels of lead and cadmium in hair samples were found near lead and zinc smelters; this was considered evidence of external exposure. No environmental determinations were made for this study.

11.5.1.3 Meza Valley, Yugoslavia. A series of Yugoslavian studies investigated exposures to lead from a mine and a smelter in the Meza Valley over a period of years (Fugas et al., 1973; Graovac-Leposavic et al. 1973; Milic et al., 1973; Djuric et al., 1971, 1972). In 1967, 24-hour lead concentrations measured four on different days varied from 13 to 84 µg/m^3 in the village nearest the smelter, and concentrations of up to 60 µg/m^3 were found as far as 5 km from the source. Mean particle size in 1968 was less than 0.8 µm. Analysis of some common foodstuffs showed concentrations that were 10-100 times higher than corresponding foodstuffs from the least exposed area (Mezica) (Djuric et al., 1971). After January, 1969, when partial control of emissions was established at the smelter, weighted average weekly exposure was calculated to be 27 µg/m^3 in the village near the smelter. In contrast to this, the city of Zagreb (Fugas et al., 1973), which has no large stationary source of lead, had an average weekly air lead level of 1.1 µg/m^3.

In 1968, the average concentration of ALA in urine samples from 912 inhabitants of 6 villages varied by village from 9.8-13 mg/l. A control group had a mean ALA of 5.2 mg/l. Data on lead in blood and the age and sex distribution of the villagers were not given (Djuric et al., 1971).

Of the 912 examined, 559 had an ALA level greater than 10 mg/l of urine. In 1969, a more extensive study of 286 individuals with ALA greater than 10 mg/l was undertaken (Graovac-Leposavic et al. 1973). ALA-U increased significantly from the previous year. When the published data were examined closely, there appeared to be some discrepancies in interpretation. The exposure from dust and from food might have been affected by the control devices, but no data were collected to establish this. In one village, Zerjua, ALA-U dropped from 21.7 to 9.4 mg/l in children 2-7 years of age. Corresponding ALA-U values for 8- to 15-year-olds and for adult men and women were reduced from 18.7 to 12.1, from 23.9 to 9.9, and from 18.5 to 9.0 mg/l, respectively. Because lead concentrations in air (Fugas et al., 1973), even after 1969, indicated an average exposure of 25 µg/m^3, it is possible that some other explanation should be sought. The author indicated in the report that the decrease in ALA-U showed "the dependence on meteorologic, topographic, and technological factors" (Graovac-Leposavic et al., 1973).

Fugas (1977) in a later report estimated the time-weighted average exposure of several populations studied during the course of this project. Stationary samplers as well as personal monitors were used to estimate the exposure to airborne lead for various parts of the day. These values were then coupled with estimated proportions of time at which these exposures held. In Table 11-66, the estimated time-weighted air lead values as well as the observed mean blood lead levels for these studied populations are presented. An increase in blood lead values occurs with increasing air lead exposure.

TABLE 11-66. MEAN BLOOD LEAD LEVELS IN SELECTED YUGOSLAVIAN POPULATIONS, BY ESTIMATED WEEKLY TIME-WEIGHTED AIR LEAD EXPOSURE

Population	N	Time-weighted air lead, (µg/m^3)	Blood lead level, (µg/dl)	
			Mean	SD
Rural I	49	0.079	7.9	4.4
Rural II	47	0.094	11.4	4.8
Rural III	45	0.146	10.5	4.0
Postmen	44	1.6	18.3	9.3
Customs officers	75	1.8	10.4	3.3
Street car drivers	43	2.1	24.3	10.5
Traffic policemen	24	3.0	12.2	5.1

Source: Fugas, 1977.

11.5.1.4 Kosovo Province, Yugoslavia. Residents living in the vicinity of the Kosovo smelter were found to have elevated blood lead levels (Popovac et al., 1982). In this area of Yugoslavia, five air monitoring stations had been measuring air lead levels since 1973. Mean air lead varied from 7.8 to 21.7 μg/m³ in 1973; by 1980 the air lead averages ranged from 21.3 to 29.2 μg/m³. In 1978 a pilot study suggested that there was a significant incidence of elevated blood lead levels in children of the area. Two major surveys were then undertaken.

In August, 1978, letters were sent to randomly selected families from the business community, hospitals or lead-related industries in the area. All family members were asked to come to a hospital for primary screening by erythrocyte protoporphyrin. A central population of comparable socioeconomic and dietary background was collected from a town without lead emissions. Blood levels were determined primarily for persons with EP greater than 8 μg/g Hgb. EP was measured by a hematofluorimeter, while blood lead was determined by the method of Fernandez using atomic absorption with graphite furnace and background correction.

Mean EP values were higher in the 1978 survey for exposed residents compared to controls in the average age group. EP values seemed to decline with age. Similar differences were noted for blood lead levels. The observed mean blood leads, ranging from 27.6 in the greater than 15 year age group to 50.9 μg/dl in the 5 to 10 year group, suggest substantial lead exposure of these residents. In the control group the highest blood lead level was 19 μg/dl. In December, 1980, a second survey was conducted to obtain a more representative sample of persons residing in the area. Letters were sent again, and 379 persons responded. EP levels were higher in all ages in 1980 versus 1978, although the differences were not statistically significant. The air lead levels increased from 14.3 μg/m³ in 1978 to 23.8 μg/m³ in 1980.

Comparing the 1980 blood lead results with the 1978 control group shows that the 1980 levels were higher in each age group. Males older than 15 years had higher mean blood lead levels than the females (39.3 versus 32.4 μg/dl).

11.5.1.5 The Cavalleri Study. Cavalleri et al. (1981) studied children in the vicinity of a lead smelter and children from a control area (4 km from the smelter). The exposed population consisted of 85 children aged 3-6 attending a nursery school and 80 primary school children aged 8 to 11. The control population was 25 nursery school children aged 3-6 and 64 primary school children aged 8-11. Since the smelter had installed filters 8 years before the study, the older children living in the smelter area had a much higher lifetime exposure.

Blood lead analysis was performed on venous samples using anodic stripping voltammetry by Morrell's method. Precision was checked over the range of 10-100 μg/dl. Reported reproducibility was also good. All samples were subsequently reanalyzed by AAS using graphite furnace and background correction by the method of Volosen. The average values obtained by the second method were quite similar to those of the first (average difference 1.4 μg/dl; correlation coefficient, 0.962).

Air was sampled for lead for 1 month at three sampling sites. The sites were located at 150 m, 300 m, and 4 km from the wall of the lead smelter. The average air lead levels were 2.32, 3.43, and 0.56 µg/m^3, respectively.

A striking difference in blood lead levels of the exposed and control populations was observed; levels in the exposed population were almost twice that in the control population. There was no significant difference between nursery school and primary school children. The geometric mean for nursery school children was 15.9 and 8.2 for exposed and control, respectively. For primary school it was 16.1 and 7.0 µg/dl. In the exposed area, 23 percent of the subjects had blood lead levels between 21 and 30 µg/dl and 3 percent greater than 31 µg/dl. No control children had blood lead levels greater than 20 µg/dl. The air leads were between 2-3 µg/m^3 in the exposed and 0.56 µg/m^3 in the control cases.

11.5.1.6 Hartwell Study. Hartwell et al. (1983) report a study of 4 primary smelters: two lead and two zinc. Study subjects were recruited in accordance with a statistical sampling plan based on diffusion modeling. Subjects were recruited to represent a variety of ages: 1-5 years, 6-18 years, 20-40 years, and, in two sites, ≥60 years. Environmental samples covering the important environmental sources of lead were obtained, as were blood samples. Unfortunately, air sampling was only conducted for about 1 month in each of the study areas. Dust, water, and soil samples were also collected and analyzed for lead. Table 11-67 summarizes the descriptive results of this study in terms of blood lead levels. Table 11-68 presents the Spearman correlation coefficient obtained.

11.5.2 Battery Plants

Studies of the effects of storage battery plants have been reported from France and Italy (Dequidt et al., 1971; De Rosa and Gobbato, 1970). The French study found that children from an industrialized area containing such a plant excreted more ALA than those living in a different area (Dequidt et al., 1971). Increased urinary excretion of lead and coproporphyrins was found in children living up to 100 m from a battery plant in Italy (De Rosa and Gobbato, 1970). Neither study gave data on plant emissions or lead in air.

11.5.3 Secondary Smelters

Zielhuis et al. (1979) studied children living in the vicinity of the Arnhem secondary lead smelter. In 1976 they recruited children to serve as subjects and controls. The children chosen were 2 and 3 years old. Parents were asked to complete a questionnaire for background information. Two-ml venous samples were collected from 17 children living less than 1 km, from 54 children living 1-2 km, and from 37 children living greater than 2 km from the smelter (control group). Blood samples were analyzed for lead by graphite furnace AAS and for

TABLE 11-67. LEVELS OF LEAD RECORDED IN HARTWELL ET AL. (1983) STUDY

Smelter	Distance from smelter	Air	Dust	Water	Soil	PbB Ages 1-5	PbB Ages 6-10
Bartlesville	3.5-24.0	131	241	6.04	34.8	10.5	12.4
	1.3-3.7	203	409	4.56	243	24.7	12.9
	0.8-4.3	299	386	6.81	829	39.6	21.8
	0.8-1.5	309	441	7.63	821	18.8	20.3
Palmerton	11.0-26.0	361	263	8.7	532	10.3	12.4
	5.4-14.5	563	201	6.0	117	11.3	10.2
	3.3-9.9	128	198	2.8	326	12.6	11.2
	0.3-2.8	278	438	1.8	331	15.9	10.3
Ajo	3.4-68.0	94	74.2	6.9	57.8	9.9	7.8
	1.0-6.4	108	60.0	11.5	64.5	10.6	7.7
	0.5-2.3	191	64.7	13.3	76.5	10.5	6.9
	0.5-1.3	256	116	3.1	94.8	9.2	6.9
Anaconda	10.0-26.0	141	235	3.10	75	21.0	19.0
	3.5-21.0	176	164	3.52	115	17.3	11.9
	2.0-11.0	91	210	3.02	294	18.9	14.3
	2.0-3.5	255	398	3.83	424	21.5	17.9

TABLE 11-68. SPEARMAN CORRELATIONS OF LEAD IN AIR, WATER, DUST, SOIL, AND PAINT WITH LEAD LEVELS IN BLOOD: BY SITE AND AGE GROUPS, 1978-1979

		Age (yr)			
		1-5	6-18	20-40	Over 60
		Blood	Blood	Blood	Blood
Bartlesville	Air	0.40*	0.22*	0.27*	0.19
	Water	0.05	0.14	0.07	0.23
	Dust	0.20	0.10	0.21	0.00
	Soil	0.33*	0.13		
	Paint	-0.06	0.06	0.07	-0.06
Palmerton	Air	-0.12	0.02	-0.12	
	Water	-0.06	0.11	-0.01	
	Dust	0.06	-0.07	-0.05	
	Soil	0.16	0.20		
	Paint	-0.02	0.06	0.23*	

*Significantly different from zero at 0.05 level.

FEP by the method of Piomelli. Air measurements for lead were made in autumn, 1976. Samples were established about 2 km northeast and about 0.4 km north of the plant. Air lead levels ranged from 0.8 to 21.6 μg/m^3 northeast and from 0.5 to 2.5 μg/m^3 north of the plant.

Blood leads were statistically significantly higher closer to the smelter. For all children the mean blood lead level was 19.7 μg/dl for the less than 1 km and 11.8 μg/dl for the controls (>2 km). Similarly, FEP levels were higher for the closer (41.9 μg/100 ml erythrocytes) children as opposed to the control (32.5 μg/100 ml RBC). Higher blood levels were associated with lower socioeconomic status.

Further investigation of this smelter was undertaken by Brunekreef et al. (1981) and Diemel et al. (1981). In May, 1978, venipuncture blood samples were collected from 95 one- to three-year-old children living within 1 km of the smelter. Blood leads were determined by graphite AAS.

Before the blood sampling, an environmental sampling program was conducted. The samples collected are listed in Table 11-69. Questionnaires were administered to collect background and further exposure information. A subset of 39 children was closely observed for 1 or 2 days for mouthing behavior. Table 11-69 also presents the overall results of the environmental sampling. As can be readily seen, there is a low exposure to airborne lead (geometric mean) 0.41 μg/m^3 with a range of 0.28-0.52 μg/m^3). Soil exposure was moderate, although high. Interior dust was high in lead (geometric mean of 967 μg/g with a maximum of 4741 μg/g). In a few homes, high paint lead levels were found. Diemel et al. (1981) extended the analysis of the environmental samples. They found that indoor pollution was lower than outside. In Arnhem, it was found that lead is carried into the homes in particulate form by sticking to shoes. Most of the lead originated from soil from gardens and street dust.

Simple correlation coefficients were calculated to investigate the relationship between log blood lead and the independent variables. Significantly, correlations were found with quantity of house dust, quantity of deposited lead indoors, observational score of dustiness, age of child, and the average number of times an object is put in the mouth. Multiple regression analyses were calculated on four separate subpopulations. Among children living in houses with gardens, the combination of soil lead level and educational level of the parents explained 23 percent of the variations of blood lead. In children without gardens, the amount of deposited lead indoors explained 26 percent of the variance. The authors found that an increase in soil lead level from 100-600 μg/g resulted in an increase in blood lead of 6.3 μg/dl.

In a Dallas, Texas, study of two secondary lead smelters, the average blood lead level of exposed children was found to be 30 μg/dl versus an average of 22 μg/dl in control children (Johanson and Luby, 1972). For the two study populations, the air and soil lead levels were 3.5 and 1.5 μg/m^3 and 727 and 255 μg/g, respectively.

TABLE 11-69. ENVIRONMENTAL PARAMETERS AND METHODS: ARNHEM LEAD STUDY, 1978[a]

Parameter	Method	Geometric mean	Range
1. Lead in ambient air (μg/m³)	High-volume samples; 24-hr measurements at 6 sites, continuously for 2 months	0.41	0.28-0.52
2. Lead in dustfall (μg/m³·day)	Standard deposit gauges; 7-day measurements at 22 sites, semicontinuously for 3 months	467	108-2210
3. Lead in soil (μg/g)	Sampling in gardens of study populations; analysis of layers from 0 to 5 cm and 5 to 20 cm	240	21-1126
4. Lead in street dust (μg/g)	Samples at 31 sites, analysis of fraction <0.3mm	690	77-2667
5. Lead in indoor air (μg/m³)	Low-volume samples; 1-month measurements in homes of study population, continuously for 2 months	0.26	0.13-0.74
6. Lead in dustfall indoors (μg/m³·day)	Greased glass plates of 30 x 40 cm; 1-month measurements in homes of study population, continuously for 3 months	7.34	1.36-42.35
7. Lead in floor dust (μg/g)	Vacuum cleaner with special filter holder; 5 samples, collected on 3 different occasions; with intervals of approximately 1 month, in homes of study populations	fine 957 course 282	463-4741 117-5250
8. Easily available lead indoors	Wet tissues, 1 sample in homes of study population	85% of samples	<20 μg Pb/tissue
9. Lead in tapwater	Proportional samples, during 1 week in homes of study population	5.0 (arithmetic) mean	<0.5-90.0
10. Dustiness of homes	Visual estimation, on a simple scale ranging from 1 (clean) to 3 (dusty); 6 observations in homes of study population		

[a] All lead analyses were performed by atomic absorption spectrophotometry, except part of the tapwater analysis, which was performed by anodic stripping voltametry. Lead in tapwater analyzed by the National Institute of Drinking Water Supply in Leidscherdam. Soil and street dust analyzed by the Laboratory of Soil and Plant Research in Oosterbeek. (Zielhuis, et. al., 1979; Diemel, et. al., 1981)

In Toronto, Canada, the effects of two secondary lead smelters on the blood and hair lead levels of nearby residents have been extensively studied (Ontario Ministry of the Environment, 1975; Roberts et al., 1974). In a preliminary report, Roberts et al. (1974) stated that blood and hair lead levels were higher in children living near the two smelters than in children living in an urban control area. Biologic and environmental lead levels were reported to decrease with increasing distance from the base of the smelter stacks.

A later and more detailed report identified a high rate of lead fallout around the two secondary smelters (Ontario Ministry of the Environment, 1975). Two groups of children living within 300 m of each of the smelters had geometric mean blood lead levels of 27 and 28 µg/dl, respectively; the geometric mean for 1231 controls was 17 µg/dl. Twenty-eight percent of the sample children tested near one smelter during the summer and 13 percent of the sample children tested near the second smelter during the winter had blood lead levels greater than 40 µg/dl. Only 1 percent of the controls had blood lead levels greater than 40 µg/dl. For children, blood lead concentrations increased with proximity to both smelters, but this trend did not hold for adults, generally. The report concluded that soil lead levels were the main determinant of blood lead levels; this conclusion was disputed by Horn (1976).

Blood lead levels in 293 Finnish individuals, aged 15-80, were significantly correlated with proximity to a secondary lead smelter (Nordman et al., 1973). The geometric mean blood lead concentration for 121 males was 18.1 µg/dl; for 172 females, it was 14.3 µg/dl. In 59 subjects who spent their entire day at home, a positive correlation was found between blood lead and distance from the smelter up to 5 km. Only one of these 59 individuals had a blood lead greater than 40 µg/dl, and none exceeded 50 µg/dl.

11.5.4 Secondary Exposure of Children

Excessive intake and absorption of lead on the part of children can result when parents who work in a dusty environment with a high lead content bring dust home on their clothes, shoes, or even their automobiles. Once they are home, their children are exposed to the dust.

Landrigan et al. (1976) reported that the 174 children of smelter workers who lived within 24 km of the smelter had significantly higher blood lead levels, a mean of 55.1 µg/dl, than the 511 children of persons in other occupations living in the same areas whose mean blood lead levels were 43.7 µg/dl. Analyses by EPA of the data collected in Idaho showed that employment of the father at a lead smelter, at a zinc smelter, or in a lead mine resulted in higher blood lead levels in the children living in the same house as opposed to those children whose fathers were employed in different locations (Table 11-70). The effect associated with parental employment appears to be much more prominent in the most contaminated study areas nearest to the smelter. This may be the effect of an intervening socioeconomic variable: the

TABLE 11-70. GEOMETRIC MEAN BLOOD LEAD LEVELS FOR CHILDREN BASED ON REPORTED OCCUPATION OF FATHER, HISTORY OF PICA, AND DISTANCE OF RESIDENCE FROM SMELTER (micrograms per deciliter)

		Lead smelter worker		Lead/zinc mine worker		Zinc smelter worker		Other occupations	
Area	Distance from smelter, km	Pica	No Pica	Pica	No Pica	Pica	No Pica	Pica	No Pica
1	1.6	78.7	74.2	75.3	63.9	69.7	59.1	70.8	59.9
2	1.6 to 4.0	50.2	52.2	46.9	46.9	62.7	50.3	37.2	46.3
3	4.0 to 10.0	33.5	33.3	36.7	33.5	36.0	29.6	33.3	32.6
4	10.0 to 24.0	-	30.3	38.0	32.5	40.9	36.9	-	39.4
5	24.0 to 32.0	-	24.5	31.8	27.4	-	-	28.0	26.4
6	75	-	-	-	-	-	-	17.3	21.4

Source: Landrigan et al. 1976.

lowest paid workers, employed in the highest exposure areas within the industry, might be expected to live in the most undesirable locations, closest to the smelter.

Landrigan et al. (1976) also reported a positive history of pica for 192 of the 919 children studied in Idaho. This history was obtained by physician and nurse interviews of parents. Pica was most common among 2-year-old children and only 13 percent of those with pica were above age 6. Higher blood lead levels were observed in children with pica than in those without pica. Table 11-70 shows the mean blood lead levels in children as they were affected by pica, occupation of the father, and distance of residence from the smelter. Among the populations living nearest to the smelter, environmental exposure appears to be sufficient at times to more than overshadow the effects of pica, but this finding may also be caused by inadequacies inherent in collecting data on pica. These data indicate that in a heavily contaminated area, blood lead levels in children may be significantly increased by the intentional ingestion of nonfood materials having a high lead content.

Data on the parents' occupation are, however, more reliable. It must be remembered also that the study areas were not homogeneous socioeconomically. In addition, the specific type of work an individual does in an industry is probably much more important than simply being employed in a particular industry. The presence in the home of an industrial employee exposed occupationally to lead may produce increases in the blood lead levels ranging from 10 to 30 percent.

The importance of the infiltration of lead dusts onto clothing, particularly the undergarments, of lead workers and their subsequent transportation has been demonstrated in a number of studies on the effects of smelters (Martin et al., 1975). It was noted in the United Kingdom that elevated blood lead levels were found in the wives and children of workers, even though they resided some considerable distance from the facility. It was most prominent in the workers themselves, who had elevated blood lead levels. Quantities of lead dust were found in workers' cars and homes. It apparently is not sufficient for a factory merely to provide outer protective clothing and shower facilities for lead workers. In another study in Bristol, 650-1400 µg/g of lead was found in the undergarments of workers as compared with 3-13 µg/g in undergarments of control subjects. Lead dust will remain on the clothing even after laundering: up to 500 mg of lead has been found to remain on an overall garment after washing (Lead Development Association, 1973).

Baker et al. (1977a) found blood lead levels greater than 30 µg/dl in 38 of 91 children whose fathers were employed at a secondary lead smelter in Memphis, TN. House dust, the only source of lead in the homes of these children, contained a mean of 2687 µg/g compared with 404 µg/g in the homes of a group of matched controls. Mean blood lead levels in the workers' children were significantly higher than those for controls and were closely correlated with the lead content of household dust. In homes with lead in dust less than 1000 µg/g, 18 children had a mean blood lead level of 21.8 ± 7.8 µg/dl, whereas in homes where lead in dust was greater than 7000 µg/g, 6 children had mean blood lead levels of 78.3 ± 34.0 µg/dl. See Section 7.3.2.1.6 for a further discussion of household dust.

Other studies have documented increased lead absorption in children of families where at least one member was occupationally exposed to lead (Fischbein et al., 1980a). The occupational exposures involved battery operations (Morton et al., 1982; U.S. Centers for Disease Control, 1977b; Dolcourt et al., 1978, 1981; Watson et al., 1978; Fergusson et al., 1981) as well as other occupations (Snee, 1982b; Rice et al., 1978).

In late summer of 1976, a battery plant in southern Vermont provided the setting for the first documented instance of increased lead absorption in children of employees in the battery industry. The data were first reported by the U.S. Centers for Disease Control (1977b) and more completely by Watson et al. (1978). Reports of plant workers exposed to high levels of lead stimulated a study of plant employees and their children in August and September, 1975. In the plant, lead oxide powder is used to coat plates in the construction of batteries. Before the study, the work setting of all 230 employees of the plant had been examined and 62 workers (22 percent) were identified as being at risk for high lead exposure. All of the high-risk workers interviewed reported changing clothes before leaving work and 90 percent of them reported showering. However, 87 percent of them stated that their work clothes were washed at home.

Of the high-risk employees, 24 had children between the ages of 1 and 6 years. A case-control study was conducted in the households of 22 of these employees. Twenty-seven children were identified. The households were matched with neighborhood controls, including 32 control children. None of the control family members worked in a lead industry. Capillary blood specimens were collected from all children and the 22 battery plant employees had venous specimens taken. All blood samples were analyzed for lead by AAS. Interviewers obtained background data, including an assessment of potential lead exposures.

About 56 percent of the employees' children had blood leads greater than 30 μg/dl compared with about 13 percent of the control children. Mean blood lead levels were significantly different, 31.8 μg/dl and 21.4 μg/dl, respectively. Blood lead levels in children were significantly correlated with employee blood lead levels.

House dust lead levels were measured in all children's homes. Mean values were 2239.1 μg/g and 718.2 μg/g for employee and control homes, respectively; this was a statistically significant difference. Examination of the correlation coefficient between soil lead and blood lead levels in the two sets of homes showed a marginally significant coefficient in the employee households but no correlation in the control homes. Tap water and paint lead levels did not account for the observed difference in blood leads between children of workers and neighborhood controls. It is significant that these findings were obtained despite the changing of clothes at the plant.

Morton et al. (1982) conducted their study of children of battery plant workers and controls during February-March, 1978. Children were included in the study if one parent had at least 1 year of occupational exposure, if they had lived at the same residence for at least 6 months, and if they were from 12-83 months of age. Children for the control group had to have no parental occupational exposure to lead for 5 years, and had to have lived at the same address at least 6 months.

Thirty-four children were control-matched to the exposed group by neighborhoods and age (±1 year). No matching was thought necessary for sex because in this age group blood lead levels are unaffected by sex. The selection of the control population attempted to adjust for both socioeconomic status as well as exposure to automotive lead.

Capillary blood specimens were collected concurrently for each matched pair. Blood lead levels were measured by the CDC lab using a modified Delves cup AAS procedure. Blood lead levels for the employees for the previous year were obtained from company records. Questionnaires were administered at the same time as the blood sampling to obtain background information. The homemaker was asked to complete the interview to try to get a more accurate picture of the hygiene practices followed by the employees.

Children's blood lead levels differed significantly between the exposed and control groups. Fifty-three percent of the employees' children had blood lead levels greater than 30 µg/dl, while no child in the control population had a value greater than 30 µg/dl. The mean blood lead for the children of the employees was 49.2 µg/dl with a standard deviation of 8.3 µg/dl. These data represent the population average for yearly individual average levels. The employees had an average greater than 60 µg/dl. Still, this is lower than the industry average. Of the eight children with blood levels greater than 40 µg/dl, seven had fathers with blood lead greater than 50 µg/dl. Yet there was not a significant correlation between children's blood lead level and father's blood lead level.

Investigations were made into the possibility that other lead exposures could account for the observed difference in blood lead levels between children of employees and control children. In 11 of the 33 pairs finally included in the study, potential lead exposures other than fathers' occupations were found in the employee child of the matched pair. These included a variety of lead sources such as automobile body painting, casting of lead, and playing with spent shell casings. The control and exposed populations were again compared after removing these 11 pairs from consideration. There was still a statistically significant difference in blood lead level between the two groups of children.

An examination of personal hygiene practices of the workers showed that within high-exposure category jobs, greater compliance with recommended lead containment practices resulted in lower mean blood lead levels in children. Mean blood leads were 17.3, 36.0, and 41.9 µg/dl for good, moderately good, and poor compliance groups, respectively. In fact, there was only a small difference between the good hygiene group within the high-exposure category and the mean of the control group (17.3 µg/dl versus 15.9 µg/dl). Insufficient sample sizes were available to evaluate the effect of compliance on medium and low lead exposures for fathers.

Dolcourt et al. (1978) investigated lead absorption in children of workers in a plant that manufactures lead-acid storage batteries. The plant became known to these researchers as a result of finding an elevated blood lead level in a 20-month-old child during routine screening. Although the child was asymptomatic, his mother proved not to be. Two siblings were also found to have elevated blood lead levels. The mother was employed by the plant; her work involved much hard labor and brought her into continual contact with powdery lead oxide. No uniforms or garment covers were provided by the company. As a result of these findings, screening was offered to all children of plant employees.

During February to May, 1977, 92 percent of 63 eligible children appeared for screening. Age ranged from 10 months to 15 years. About equal numbers of girls and boys underwent screening. Fingerstick blood samples were collected on filter paper and were analyzed for lead by AAS. Children with blood lead levels equal to or greater than 40 µg/dl were referred for more detailed medical evaluation including an analysis of a venous blood specimen for lead. Dust samples were collected from carpeting in each home and analyzed for lead by graphite furnace AAS. Home tap water was analyzed for lead by AAS, and house paint was analyzed for lead by XRF.

Of the 58 children who had the initial fingerstick blood lead elevation, 69 percent had blood lead levels equal to or greater than 30 µg/dl. Ten children from six families had blood lead levels equal to or greater than 40 µg/dl, and blood lead levels were found to vary markedly with age. The 0- to 3-year-old category exhibited the highest mean (48.6 µg/dl) with the 3- to 6-year-olds the next highest (38.2 µg/dl). Lowest mean values were found in the equal to or greater than 10-year-old group (26.7 µg/dl).

More detailed investigation of the six families with the highest blood lead levels in their children revealed the following: five of the six lived in rural communities, with no pre-existing source of lead from water supply, house paint, industrial emissions, or heavy automobile traffic. However, dust samples from the carpets exhibited excessively high lead concentrations. These ranged from 1700 to 84,050 µg/g.

Fergusson et al. (1981) sampled three population groups: general population, employees of a battery plant, and children of battery plant employees, using hair lead levels as indices of lead. Hair lead levels ranged from 1.2 to 110.9 µg/g in the 203 samples from the general population. The distribution of hair lead levels was nearly lognormal. Employees of the battery factory had the highest hair lead levels (median ~250 µg/g), while family members (median ~40 µg/g) had a lesser degree of contamination and the general population (median ~5 µg/g) still less.

Analysis of variance results indicated a highly significant difference between mean lead levels of the general survey and family members of the employees, and a significant difference between the mean lead levels in the hair of the employees and their families. No significant differences were found comparing mean hair lead levels among family members in terms of age and sex. The analyses of the house dust suggested that the mechanism of exposure of family members is via the lead in dust that is carried home. Mean dust lead level among the homes of factory employees was 5580 µg/g while the dust inside of houses along a busy road was only 1620 µg/g. Both of these concentrations are for particles less than 0.1 mm.

Dolcourt et al. (1981) reported two interesting cases of familial exposure to lead caused by recycling of automobile storage batteries. The first case was of a 22-member, four-generation family living in a three-bedroom house in rural eastern North Carolina. The great-grandfather of the index case worked at a battery recycling plant. He had two truckloads of spent casings delivered to the home to serve as fuel for the wood stove; the casings were burned over a 3-month period.

The index case presented with classic signs of acute lead encephalopathy, the most severe and potentially fatal form of acute lead poisoning. The blood lead level was found to be 220 μg/dl. Three months after initial diagnosis and after chelation therapy, she continued to have seizures and was profoundly mentally retarded. Dust samples were obtained by vacuum cleaner and analyzed for lead by flameless AAS. Dust from a sofa near the wood stove contained 13,283 μg/g lead, while the kitchen floor dust had 41,283 μg/g. There was no paint lead. All other members of the family had elevated blood lead levels ranging from 27-256 μg/dl.

The other case involved a truck driver working in a low-exposure area of a battery recycling operation in rural western North Carolina. He was operating an illegal battery recycling operation in his home by melting down reclaimed lead on the kitchen stove. No family member was symptomatic for lead symptoms but blood lead levels ranged from 24 to 72 μg/dl. Soil samples taken from the driveway, which was paved with fragments of the discarded battery casings, contained 12-13 percent lead by weight.

In addition to families being exposed as a result of employment at battery plants, studies have been reported recently for smelter worker families (Rice et al., 1978; Snee, 1982c). Rice et al. studied lead contamination in the homes of secondary lead smelters. Homes of employees of secondary smelters in two separate geographic areas of the country were examined to determine whether those homes had a greater degree of lead contamination than homes of workers in the same area not exposed to lead. Both sets of homes (area I and II) were examined at the same time of the year.

Thirty-three homes of secondary smelter employees were studied; 19 homes in the same or similar neighborhoods were studied as controls. Homes studied were in good condition and were one- or two-family dwellings. Blood lead levels were not obtained for children in these homes. In the homes of controls, a detailed occupational history was obtained for each employed person. Homes where one or more residents were employed in a lead-contaminated environment were excluded from the analysis.

House dust samples were collected by Vostal's method and were analyzed for lead by AAS. In one of the areas, samples of settled dust were collected from the homes of employees and controls. Dust was collected over the doorways. In homes where the settled dust was collected, zinc protoporphyrin (ZPP) determinations were made in family members of the lead workers and in the controls.

In both areas, the wipe samples were statistically significantly higher in the homes of employees compared to controls (geometric mean 79.3 ± 61.8 μg/g versus 28.8 ± 7.4 μg/g Area I; 112.0 ± 2.8 μg/g versus 9.7 ± 3.9 μg Area II). No significant differences were found between workers' homes or controls between Area I and Area II. Settled dust lead was significantly higher in the homes of employees compared to controls (3300 versus 1200 μg/g). Lead contents of particulate matter collected at the curb and of paint chips collected in the home were not significantly different between employee homes and controls. Zinc protoporphyrin determinations were done on 15 children, 6 years or younger. ZPP levels were higher in employee children than in control children. Mean levels were 61.4 μg/ml and 37.6 μg/ml, respectively.

It should be noted again that the wipe samples were not different between employee homes in the two areas. Interviews with employees indicated that work practices were quite similar in the two areas. Most workers showered and changed before going home. Work clothes were washed by the company. Obviously, much closer attention needs to be paid to other potential sources of lead introduction into the home (e.g., automobile surfaces).

From Mexico (Molina-Ballesteros et al., 1983) comes a report of yet another occupation which can contribute to the lead burden of children whose parents work in settings contaminated by lead. One hundred and fifty-three children belonging to pottery-making families with home workshops were studied, as well as 80 randomly selected children serving as controls. Venipuncture blood samples were collected and analyzed by atomic absorption spectrophotometry. Mean blood lead levels were 15 μg/dl higher for children whose parents had the home pottery workshops than for control children. The mean blood lead level in the exposed children was 39.5 μg/dl, which indicates a high degree of lead absorption in these children.

11.5.5 Miscellaneous Studies

11.5.5.1 Studies Using Indirect Measures of Air Exposure.

11.5.5.1.1 Studies in the United States. A 1973 Houston study examined the blood lead levels of parking garage attendants, traffic policemen, and adult females living near freeways (Johnson et al., 1974). A control group for each of the three exposed populations was selected by matching for age, education, and race. Unfortunately, the matching was not altogether successful; traffic policemen had less education than their controls, and the garage employees were younger than their controls. Females were matched adequately, however. It should be noted that the mean blood lead values for traffic policemen and parking garage attendants, two groups regularly exposed to higher concentrations of automotive exhausts, were significantly higher than the means for their relevant control groups. Statistically significant differences in mean values were not found, however, between women living near a freeway, and control women living at greater distances from the freeway.

A study of the effects of lower-level urban traffic densities on blood lead levels was undertaken in Dallas, Texas, in 1976 (Johnson et al., 1978). The study consisted of two phases. One phase measured air lead values for selected traffic densities and conditions, ranging from equal to or less than 1,000 to about 37,000 cars/day. The second phase consisted of an epidemiological study of traffic density and blood lead levels among residents. Figure 11-31 shows the relationship between arithmetic means of air lead and traffic density. As can be seen from the graph, a reasonable fit was obtained.

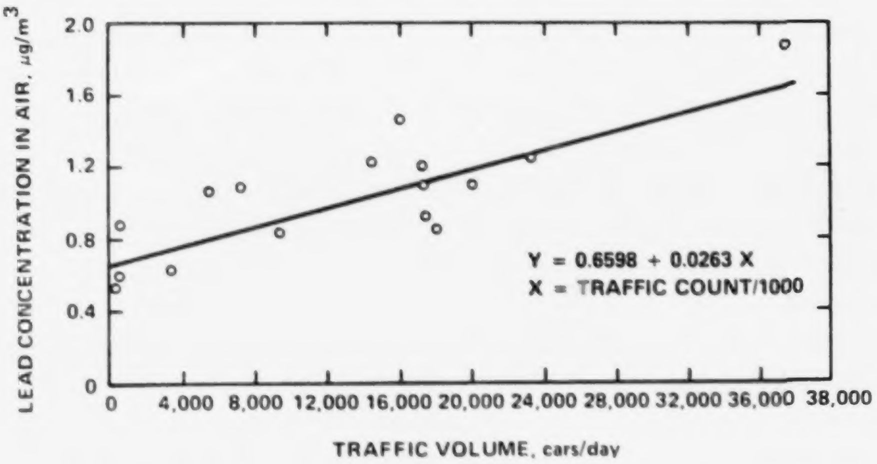

Figure 11-31. Arithmetic mean of air lead levels by traffic volume. Dallas, 1976.

Source: Johnson et al. (1978).

In addition, for all distances measured (1.5-30.5 m from the road), air lead concentrations declined rapidly with distance from the street. At 15 m, concentrations were about 55 percent of the street concentrations. In air lead collections from 1.5 to 30.5 m from the street, approximately 50 percent of the airborne lead was in the respirable range (<1 µm), and the proportions in each size class remained approximately the same as the distance from the street increased.

Soil lead concentrations were higher in areas with greater traffic density, ranging from 73.6 µg/g at less than 1,000 cars per day to a mean of 105.9 at greater than 19,500 cars per day. The maximum soil level obtained was 730 µg/g. Dustfall samples for 28 days from nine locations showed no relationship to traffic densities, but outdoor levels were at least 10 times the indoor concentration in nearby residences.

In the second phase, three groups of subjects, 1 to 6 years old, 18 to 49 years old, and 50 years and older, were selected in each of four study areas. Traffic densities selected were less than 1,000, 8,000-14,000, 14,000-20,000, and 20,000-25,000 cars/day. The study groups averaged about 35 subjects, although the number varied from 21 to 50. The smallest groups were from the highest traffic density area. No relationship between traffic density and blood lead levels in any of the age groups was found (Figure 11-32). Blood lead levels were significantly higher in children, 12-18 µg/dl, than in adults, 9-14 µg/dl.

Caprio et al. (1974) compared blood lead levels and proximity to major traffic arteries in a study reported in 1971 that included 5226 children in Newark, New Jersey. Over 57 percent of the children living within 30.5 m of roadways had blood lead levels greater than 40 µg/dl. For those living between 30.5 and 61 m from the roadways, more than 27 percent had such levels, and at distances greater than 61 m, 31 percent exceeded 40 µg/dl. The effect of automobile traffic was seen only in the group that lived within 30.5 m of the road.

No other sources of lead were considered in this study. However, data from other studies on mobile sources indicate that it is unlikely that the blood lead levels observed in this study resulted entirely from automotive exhaust emissions.

In 1964, Thomas et al. (1967) investigated blood lead levels in 50 adults who had lived for at least 3 years within 76 m of a freeway (Los Angeles) and those of 50 others who had lived for a similar period near the ocean or at least 1.6 km from a freeway. Mean blood lead levels for those near the freeway were 22.7 ± 5.6 for men and 16.7 ± 7.0 µg/dl for women. These concentrations were higher than for control subjects living near the ocean: 16.0 ± 8.4 µg/dl for men and 9.9 ± 4.9 µg/dl for women. The higher values, however, were similar to those of other Los Angeles populations. Measured mean air concentrations of lead in Los Angeles for October, 1964, were as follows: 12.25 ± 2.70 µg/m^3 at a location 9 m from the San Bernardino freeway; 13.25 ± 1.90 µg/m^3 at a fourth-floor location 91.5 m from the freeway; and 4.60 ± 1.92 µg/m^3 1.6 km from the nearest freeway. The investigators concluded that the differences observed were consistent with coastal inland atmospheric and blood lead gradients in the Los Angeles basin and that the effect of residential proximity to a freeway (7.6-76 m) was not demonstrated.

Ter Haar and Chadzynski report a study of blood lead levels of children living near three heavily travelled streets in Detroit (Ter Haar, 1981; Ter Haar and Chadzynski, 1979). Blood lead levels were not found to be related to distance from the road but were related to conditions of housing and age of the child after multiple regression analyses.

11.5.5.1.2 British studies. In a Birmingham, England, study, mean blood lead levels in 41 males and 58 females living within 800 m of a highway interchange were 14.41 and 10.93 µg/dl, respectively, just before the opening of the interchange in May, 1972 (Waldron, 1975). From

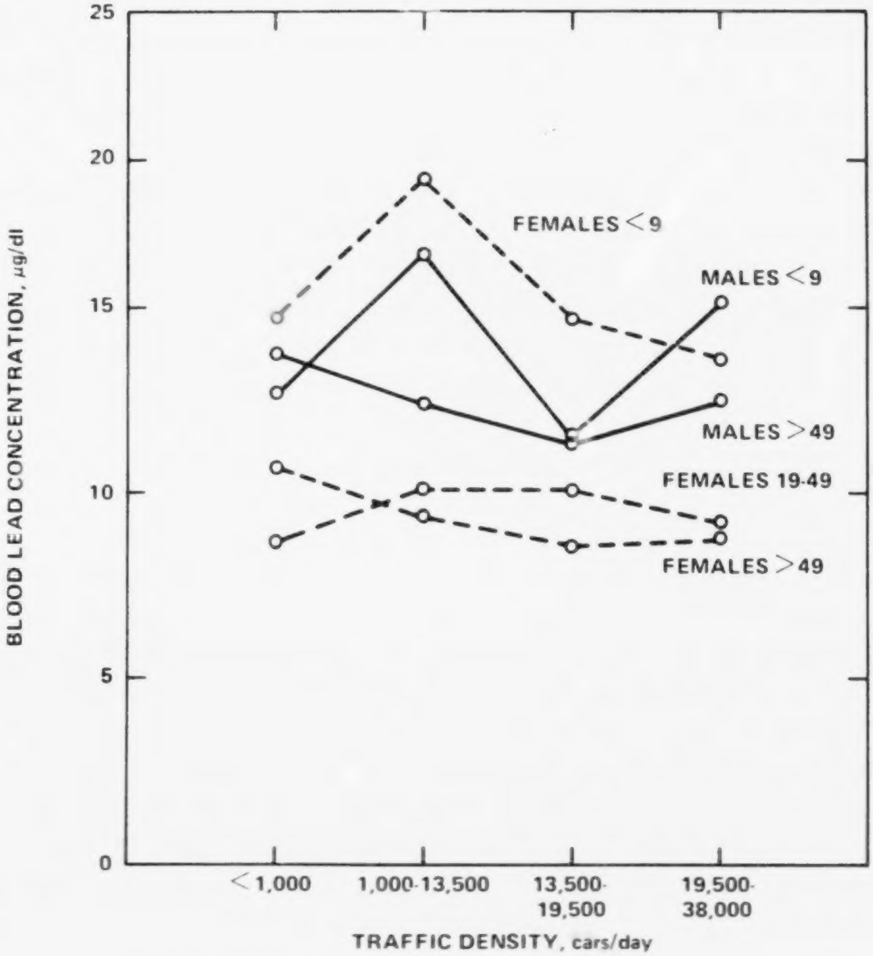

Figure 11-32. Blood lead concentration and traffic density by sex and age, Dallas, 1976.

Source: Johnson et al. (1978).

October, 1972, to February, 1973, the respective values for the same individuals were 18.95 and 14.93 µg/dl. In October, 1973, they were 23.73 and 19.21 µg/dl. The investigators noted difficulties in the blood collection method during the baseline period and changed from capillary to venous blood collection for the remaining two sets of samples. To interpret the significance of the change in blood collection method, some individuals gave both capillary and venous blood at the second collection. The means for both capillary and venous bloods were calculated for the 18 males and 23 females who gave both types of blood samples (Barry, 1975). The venous blood mean values for both these males and females were lower by 0.8 and 0.7 µg/dl, respectively. If these differences were applied to the means of the third series, the mean for males would be reduced to 24.8 µg/dl and that for the females to 18.7 µg/dl. These adjusted means still show an increase over the means obtained for the first series. Comparing only the means for venous bloods, namely series two and three, again shows an increase for both groups. The increase in blood lead values was larger than expected following the model of Knelson et al. (1973), because air lead values near the road were approximately 1 µg/m^3. The investigators concluded that either the lead aerosol of very small particles behaved more like a gas so that considerably more than 37 percent of inhaled material was absorbed, or that ingestion of lead-contaminated dust might be responsible.

Studies of taxicab drivers have employed different variables to represent the drivers' lead exposure (Flindt et al., 1976; Jones et al., 1972): one variable was night versus day-shift drivers (Jones et al., 1972); the other was mileage driven (Flindt et al., 1976). No difference was observed, in either case.

The studies reviewed show that automobiles produce sufficient emissions to increase air and nearby soil concentrations of lead as well, and to increase blood lead concentrations in children and adults. The problem is of greater importance when houses are located within 100 ft (30 m) of the roadway.

11.5.5.2 Miscellaneous Sources of Lead. The habit of cigarette smoking is a source of lead exposure. Shaper et al. (1982) report that blood lead concentration is higher for smokers than nonsmokers and that cigarette smoking makes a significant independent contribution to blood lead concentration in middle-aged men in British towns. A direct increase in lead intake from cigarettes is thought to be responsible. Hopper and Mathews (1983) comment that current smoking has a significant effect on blood lead level, with an average increase of 5.8 percent in blood lead levels for every 10 cigarettes smoked per day. They also report that past smoking history had no measurable effect on blood lead levels. Hasselblad and Nelson (1975) report an average increase in women's blood lead levels of 1.3 µg/dl for smokers compared to nonsmokers in the study of Tepper and Levin (1975).

Although no studies are available, it is conceivable that destruction of lead-containing plastics (to recover copper), which has caused cattle poisoning, also could become a source of lead exposure for humans. Waste disposal is a more general problem because lead-containing materials may be incinerated and may thus contribute to increased air lead levels. This source of lead has not been studied in detail. Tyrer (1977) cautions of the lead hazard in the recycling of waste.

The consumption of illicitly distilled liquor has been shown to produce clinical cases of lead poisoning. Domestic and imported earthenware (De Rosa et al., 1980) with improperly fired glazes have also been related to clinical lead poisoning. This source becomes important when foods or beverages high in acid are stored in earthenware containers, because the acid releases lead from the walls of the containers.

Particular cosmetics, popular among some Oriental and Indian ethnic groups, contain high percentages of lead that sometimes are absorbed by users in quantities sufficient to be toxic. Ali et al. (1978) and Attenburrow et al. (1980) discuss the practice of surma and lead poisoning. In addition to lead-containing cosmetics causing lead poisoning, folk remedies have also been linked to lead poisoning (U. S. Centers for Disease Control, 1983a,b). Two Mexican folk remedies, Azarcon and greta, have been implicated as causing lead poisoning in children (U.S. Centers for Disease Control, 1983a). These products have a high lead content (70-90 percent) and are primarily lead tetroxide and lead oxide for Azarcon and greta, respectively. There have been a minimum of 15 reported cases of lead poisoning associated with these products. A survey of Mexican-Hispanics living in Los Angeles estimated that 7.1-21.1 percent of Mexican-Hispanic households had at some time used these products.

A folk medicine used by Hmong refugees from Northern Laos has also been implicated in lead poisoning of children (U.S. Centers for Disease Control, 1983b). The product, "pay-loo-ah," has a variable composition and texture, making control more difficult. Other sources of lead are presented in Table 11-71.

TABLE 11-71. SOURCES OF LEAD

Source	References
Gasoline sniffing	Kaufman and Wiese (1978) Coodin and Boeckx (1978) Hansen and Sharp (1978)
Colored gift wrapping	Bertagnolli and Katz (1979)
Gunshot wound	Dillman et al. (1979)
Drinking glass decorations	Anonymous (1979)
Electric kettles	Wigle and Charlebois (1978)
Hair dye	Searle and Harnden (1979)
Snuff use	Filippini and Simmler (1980)
Firing ranges	Fischbein et al. (1979, 1980b)
Glazed pottery	Acra et al. (1981)

11.6 SUMMARY AND CONCLUSIONS

Using the bones and teeth of ancient populations, studies show that levels of internal exposures of lead today are substantially elevated over past levels. Studies of current populations living in remote areas far from urbanized cultures show blood lead levels in the range of 1-5 μg/dl. In contrast to the blood lead levels found in remote populations, data from current U.S. populations have geometric means ranging from <10 to 20 μg/dl depending on age, race, sex, and degree of urbanization. These higher current exposure levels appear to be associated with industrialization and widespread commercial use of lead, e.g., in gasoline combustion.

Age appears to be one of the single most important demographic covariates of blood lead levels. Blood lead levels in children up to six years of age are generally higher than those in non-occupationally exposed adults. Children aged two to three years tend to have the highest levels, as shown in Figure 11-33. Blood lead levels in non-occupationally exposed adults may increase slightly with age due to skeletal lead accumulation.

Sex has a differential impact on blood lead levels depending on age. No significant differences exist between males and females less than seven years of age. Males above the age of seven generally have higher blood lead levels than females.

Race also plays a role, in that blacks generally have higher blood lead levels than either whites or Hispanics and urban black children (aged 6 months-5 years) have markedly higher blood lead concentrations than any other racial or age group. Possible genetic factors associated with race have yet to be fully untangled from differential exposure levels and other factors as important determinants of blood lead levels.

Blood lead levels also generally increase with degree of urbanization. Data from NHANES II show blood lead levels in the United States, averaged over 1976-1980, increasing from a geometric mean of 11.9 μg/dl in rural populations to 12.8 μg/dl in urban populations of less than one million, and increasing again to 14.0 μg/dl in urban populations of one million or more.

Blood lead levels, examined on a population basis, have similarly skewed distributions. Blood lead levels, from a population thought to be homogeneous in terms of demographic and lead exposure characteristics, approximately follow a lognormal distribution. The geometric standard deviations, an estimation of dispersion, for four different studies are shown in Table 11-72. The values, including analytic error, are about 1.4 for children and possibly somewhat smaller for adults. This allows an estimation of the upper tail of the blood lead distribution, the group at higher risk. A somewhat larger geometric standard deviation of 1.42 may be derived from the NHANES II study when only gasoline and industrial air lead emission exposures are assumed to be controllable sources of variation.

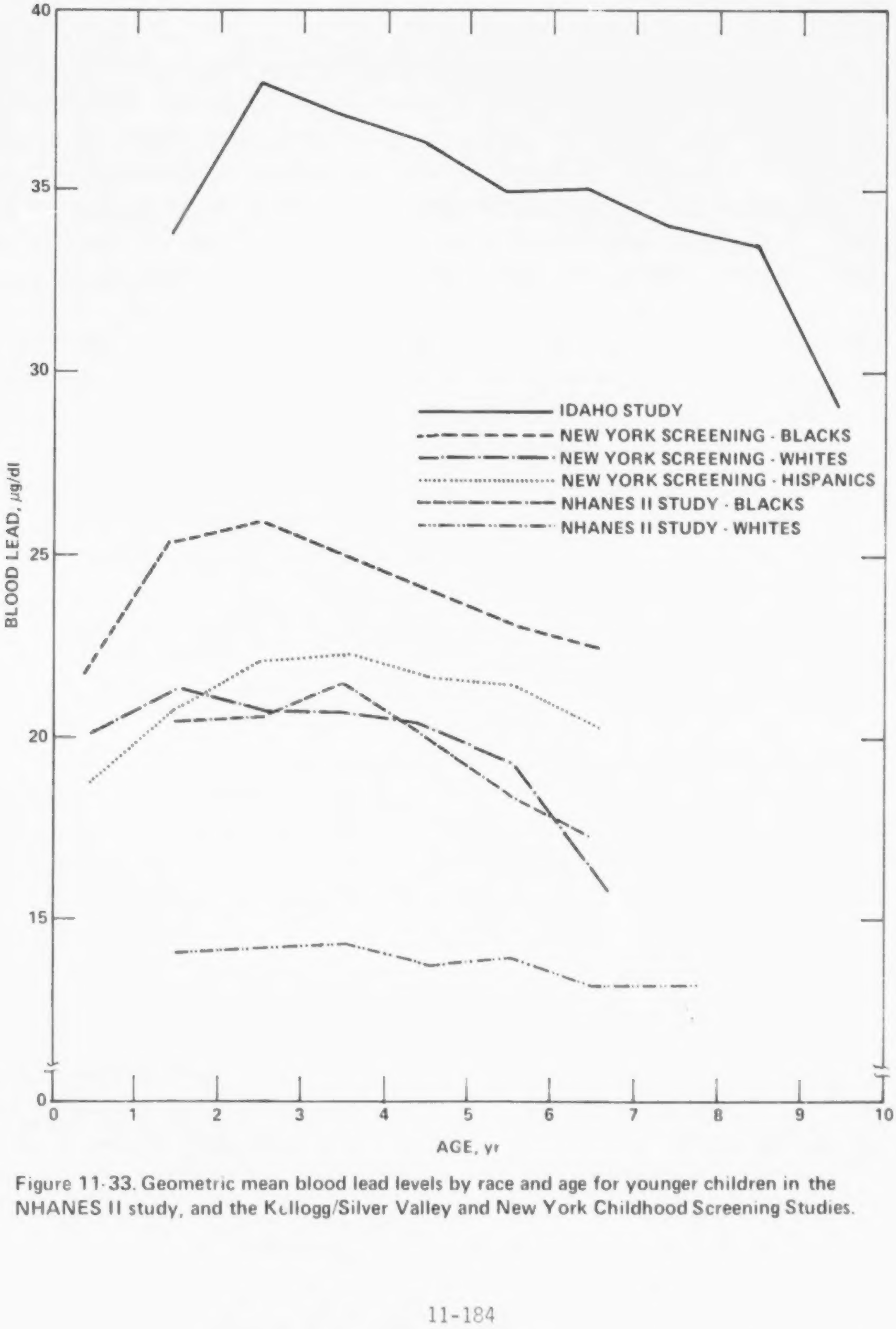

Figure 11-33. Geometric mean blood lead levels by race and age for younger children in the NHANES II study, and the Kellogg/Silver Valley and New York Childhood Screening Studies.

TABLE 11-72. SUMMARY OF BLOOD LEAD POOLED GEOMETRIC STANDARD DEVIATIONS AND ESTIMATED ANALYTIC ERRORS

Study	Pooled geometric standard deviations				Estimated analytic error
	Inner city black children	Inner city white children	Adult females	Adult males	
NHANES II	1.37[a]	1.39[a]	1.36[b]	1.40[b]	0.021
N.Y. Childhood Screening Study	1.41	1.42	-	-	-[c]
Tepper-Leven	-	-	1.30	-	0.056[d]
Azar et al.	-	-	-	1.29	0.042[d]

Note: To calculate an estimated person-to-person GSD, compute $\mathrm{Exp}\left[\left((\ln(\mathrm{GSD}))^2 - \text{Analytic Error}\right)^{1/2}\right]$

[a] A geometric standard deviation of 1.42 may be derived when only gasoline and industrial air lead emission exposures are assumed to be controllable sources of variability.

[b] Pooled across areas of differing urbanization

[c] Not known, assumed to be similar to NHANES II

[d] Taken from Lucas (1981).

Recent U.S. blood lead levels show a downward temporal trend occurring consistently across race, age, and geographic location. The downward pattern commenced in the early part of the 1970's and has continued into 1980. The downward trend has occurred from a shift in the entire distribution and not through a truncation in the high blood lead levels. This consistency suggests a general causative factor, and attempts have been made to identify the causative element. Reduction in lead emitted from the combustion of leaded gasoline is a prime candidate.

Studies of data from blood lead screening programs (i.e., New York City) suggest that the downward trend in blood lead levels noted earlier is due to the reduction in air lead levels, which has been attributed to the reduction of lead in gasoline. The NHANES II analysis found a highly significant association between the declining blood lead concentrations for the overall U.S. population and decreasing amounts of lead used in gasoline in the United States during the same time period. Two studies used isotope ratios of lead to estimate the relative proportion of lead in the blood coming from airborne lead. From one study, by Manton, it can be estimated that between 7 and 41 percent of the blood lead in study subjects in Dallas resulted from airborne lead. Additionally, these data provide a means of estimating the indirect contribution of air lead to blood lead. By one estimate, only 10 - 20 percent of the total airborne contribution in Dallas is from direct inhalation.

From the ILE data in Facchetti and Geiss (1982) and Facchetti (1985), as shown in Table 11-73, the direct inhalation of air lead may account for 60 percent of the total adult blood lead uptake from leaded gasoline in a large urban center, but inhalation is a much less important pathway in suburban parts of the region (19 percent of the total gasoline lead contribution) and in the rural parts of the region (9 percent of the total gasoline lead contribution). EPA analyses of the preliminary results from the ILE study separated the inhalation and non-inhalation contributions of leaded gasoline to blood lead into the following three parts: (1) an increase of about 1.7 μg/dl in blood lead per μg/m^3 of air lead, attributable to direct inhalation of the combustion products of leaded gasoline; (2) a sex difference of about 2 μg/dl attributable to lower exposure of women to indirect (non-inhalation) pathways for gasoline lead; and (3) a non-inhalation background attributable to indirect gasoline lead pathways, such as ingestion of dust and food, increasing from about 2 μg/dl in Turin to 3 μg/dl in remote rural areas. The non-inhalation background represents only two to three years of environmental accumulation at the new experimental lead isotope ratio. It is not clear how to numerically extrapolate these estimates to U.S. subpopulations; but it is evident that even in rural and suburban parts of a metropolitan area, the indirect (non-inhalation) pathways for exposure to leaded gasoline make a significant contribution to blood lead. This can be seen in Table 11-73. It should also be noted that the blood lead isotope ratio responded fairly rapidly when the lead isotope ratio returned to its pre-experimental value, but it is not yet possible to estimate the long-term change in blood lead attributable to persistent exposures to accumulated environmental lead.

The strongest kind of scientific evidence about causal relationships is based on an experiment in which all possible extraneous factors are controlled. The evidence derived from the Isotopic Lead Experiment (ILE) comes very close to this ideal. The experimental inter vention consisted of replacing the normal ^{206}Pb/^{207}Pb isotope ratio by a very different ratio. There is no plausible mechanism by which other concurrent lead exposure variables (food, water and beverages, paint, and industrial emissions) could have also changed their isotope ratios. Hence the very large changes in isotope ratios in blood were responding to the change in gasoline. There was no need to carry out detailed aerometric and ecological modeling to track the leaded gasoline isotopes through the various environmental pathways. In fact, our analyses (Section 11.3.6.2.1) show that consideration of inhalation of community air lead alone will substantially under estimate the total effect of gasoline lead, at least in the 35 subjects whose blood leads were tracked in the ILE Preliminary Study. This may be partially explained by the differences in the lead concentration measured by stationary monitors

TABLE 11-73. ESTIMATED CONTRIBUTION OF LEADED GASOLINE TO BLOOD LEAD BY INHALATION AND NON-INHALATION PATHWAYS

Location	Air lead fraction from gasoline[a]	Blood lead fraction from gasoline[b]	Blood lead from gasoline in air[c] (μg/dl)	Blood lead not inhaled from gasoline[d] (μg/dl)	Estimated fraction gas-lead inhalation[e]
Turin	0.873	0.214	2.79	1.88	0.60
<25 km	0.587	0.114	0.53	2.33	0.19
>25 km	0.587	0.101	0.28	2.93	0.09

[a] Fraction of air lead in Phase 2 attributable to lead in gasoline.
[b] Mean fraction of blood lead in Phase 2 attributable to lead in gasoline.
[c] Estimated blood lead from gasoline inhalation = $\beta \times a \times b$, $\beta = 1.6$.
[d] Estimated blood lead from gasoline, non-inhalation = f-e.
[e] Fraction of blood lead uptake from gasoline attributable to direct inhalation = f/e.

Source: Facchetti and Geiss (1982), pp. 52-56; Facchetti (1985).

compared to those that would be measured by personal monitors, expecially if higher exposures occur in certain microenvironments. Diet lead is also an explanation for the large excess of gasoline lead isotope ratio in blood beyond that expected from inhalation of ambient air lead, both from gasoline lead entering the food chain and added by food processing and preparation. The subjects in the ILE study cannot be said to represent some defined population, and it is not clear how the results can be extended to U.S. populations. Turin's unusual meteorology, high lead levels, and "reversed" urban-rural gradient of the subjects in the ILE study indicate the need for future research. But in spite of the variable gasoline lead exposures of the subjects, there is strong evidence that changes in gasoline lead produce large changes in blood lead.

Because the main purpose of this chapter is to examine relationships of lead in air and lead in blood under ambient conditions, the results of studies most appropriate to this area have been emphasized. A summary of the most appropriate studies appears in Table 11-74. At air lead exposures of 3.2 $\mu g/m^3$ or less, there is no statistically significant difference between curvilinear and linear blood lead inhalation relationships. At air lead exposures of 10 $\mu g/m^3$ or more, either nonlinear or linear relationships can be fitted. Thus, a reasonably consistent picture emerges in which the blood lead to air lead relationship by direct inhalation was approximately linear in the range of normal ambient exposures of 0.1-2.0 $\mu g/m^3$ (as discussed in Chapter 7). Differences among individuals in a given study (and among several

TABLE 11-74. SUMMARY OF BLOOD INHALATION SLOPES, (β) μg/dl per μg/m³

Population	Study	Study type	N	(β) Slope, μg/dl per μg/m³	Model sensitivity of slope*
Children	Angle and McIntire, 1979 Omaha, NE	Population	1074	1.92	(1.40 - 4.40)[a,b,c]
Children	Roels et al. (1980) Belgium	Population	148	2.46	(1.55 - 2.46)[a,b]
Children	Yankel et al. (1977); Walter et al. (1980) Idaho	Population	879	1.52	(1.07 - 1.52)[a,b,c]
Adult males	Azar et al. (1975). Five groups	Population	149	1.32	(1.08 - 2.39)[b,c]
Adult males	Griffin et al. (1975), NY prisoners	Experiment	43	1.75	(1.52 - 3.38)[d]
Adult males	Gross (1979)	Experiment	6	1.25	(1.25 - 1.55)[b]
Adult males	Rabinowitz et al. (1973,1976, 1977)	Experiment	5	2.14	(2.14 - 3.51)[e]

*Selected from among the most plausible statistically equivalent models. For nonlinear models, slope at 1.0 μg/m³.

[a] Sensitive to choice of other correlated predictors such as dust and soil lead.

[b] Sensitive to linear versus nonlinear at low air lead.

[c] Sensitive to age as a covariate.

[d] Sensitive to baseline changes in controls.

[e] Sensitive to assumed air lead exposure.

studies) are large, so that pooled estimates of the blood lead inhalation slope depend upon the weight given to various studies. Several studies were selected for analysis, based upon factors described earlier. EPA analyses* of experimental and clinical studies (Griffin et al., 1975; Rabinowitz et al., 1974, 1976, 1977; Kehoe 1961a,b,c; Gross, 1981; Hammond et al., 1981) suggest that blood lead in adults increases by 1.64 ± 0.22 μg/dl from direct inhalation of each additional $\mu g/m^3$ of air lead. EPA analysis of Azar's population study (Azar et al., 1975) yields a slope of 1.32 ± 0.38 for adult males. EPA analyses of population studies (Yankel et al., 1977; Roels et al., 1980; Angle and McIntire, 1979) suggest that, for children, the median blood lead increase is 1.97 μg/dl per $\mu g/m^3$ for inhaled air lead.

These slope estimates are based on the assumption that an equilibrium level of blood lead is achieved within a few months after exposure begins. This is only approximately true, since lead stored in the skeleton may return to blood after some years. Chamberlain et al. (1978) suggest that long-term inhalation slopes should be about 30 percent larger than these estimates. Inhalation slopes quoted here are associated with a half-life of blood lead in adults of about 30 days. O'Flaherty et al. (1982) suggest that the blood lead half-life may increase slightly with duration of exposure, but this has not been confirmed (Kang et al., 1983).

One possible approach would be to regard all inhalation slope studies as equally informative and to calculate an average slope using reciprocal squared standard error estimates as weights. This approach has been rejected for two reasons. First, the standard error estimates characterize only the internal precision of an estimated slope, not its representativeness (i.e., bias) or predictive validity. Secondly, experimental and clinical studies obtain more information from a single individual than do population studies. Thus, it may not be appropriate to combine the two types of studies.

Estimates of the inhalation slope for children are only available from population studies. The importance of dust ingestion as a non-inhalation pathway for children is established by many studies. A pooled slope estimate, 1.97 ± 0.39, has been derived for air lead inhalation based on those studies (Angle and McIntire, 1979; Roels et al., 1980; Yankel et al., 1977) from which the air inhalation and dust ingestion contributions can both be estimated. Aggregate analyses of data from these and several other studies typically yield slope estimates in the range of 3-5 for the combined impact of both direct (inhaled) and indirect (via dust, etc.) contributions of air lead to blood lead in children.

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*Note: The term EPA analyses refers to calculations done at EPA. A brief discussion of the methods used is contained in Appendix 11-B; more detailed information is available at EPA upon request.

While direct inhalation of air lead is stressed, this is not the only air lead contribution that needs to be considered. Smelter studies allow partial assessment of the air lead contributions to soil, dust, and finger lead. Conceptual models allow preliminary estimation of the propagation of lead through the total food chain as shown in Chapter 7. Useful mathematical models to quantify the propagation of lead through the food chain need to be developed. The direct inhalation relationship does provide useful information on changes in blood lead as responses to changes in air lead on a time scale of several months. The indirect pathways through dust and soil and through the food chain may thus delay the total blood lead response to changes in air lead, perhaps by one or more years. The Italian ILE study facilitates partial assessment of this delayed response from leaded gasoline as a source.

Dietary absorption of lead varies greatly from one person to another and depends on the physical and chemical form of the carrier, on nutritional status, and on whether lead is ingested with food or between meals. These distinctions are particularly important for consumption by children of leaded paint, dust, and soil. Typical values of 10 percent absorption of ingested lead into blood have been assumed for adults and 25 to 50 percent for children.

It is difficult to obtain accurate dose-response relationships between blood lead levels and lead levels in food or water. Dietary intake must be estimated by duplicate diets or fecal lead determinations. Water lead levels can be determined with some accuracy, but the varying amounts of water consumed by different individuals add to the uncertainty of the estimated relationships.

Quantitative analyses relating blood lead levels and dietary lead exposures have been reported. Studies on infants provide estimates that are in close agreement. Only one individual study is available for adults (Sherlock et al. 1982); another estimate from a number of pooled studies is also available. These two estimates are in good agreement. Most of the subjects in the Sherlock et al. (1982) and United Kingdom Central Directorate on Environmental Pollution (1982) studies received quite high dietary lead levels (>300 μg/day). The fitted cube root equations give high slopes at lower dietary lead levels. On the other hand, the linear slope of the United Kingdom Central Directorate on Environmental Pollution (1982) study is probably an underestimate of the slope at lower dietary lead levels. For these reasons, the Ryu et al. (1983) study is the most believable, although it only applies to infants and also probably underestimates to some extent the value of the slope. Estimates for adults should be taken from the experimental studies or calculated from assumed absorption and half-life values. Most of the dietary intake supplements were so high that many of the subjects had blood lead concentrations much in excess of 30 μg/dl for a considerable part of the experiment. Blood lead levels thus may not completely reflect lead exposure, due to the previously noted nonlinearity of blood lead response at high exposures. The slope estimates for adult dietary intake are about 0.02 µg/dl increase in blood lead per µg/day intake, but consideration of blood lead kinetics may increase this value to about 0.04. Such values are a bit lower than slopes of about 0.05 µg/dl per µg/day estimated from the population studies extrapolated to typical dietary intakes. The value for infants is larger.

The relation between blood lead and water lead is not clearly defined and is often described as nonlinear. Water lead intake varies greatly from one person to another. It has been assumed that children can absorb 25-50 percent of lead in water. Many authors chose to fit cube root models to their data, although polynomial and logarithmic models were also used. Unfortunately, the form of the model greatly influences the estimated contributions to blood leads from relatively low water lead concentration.

Although there is close agreement in the quantitative analyses of the relationship between blood lead level and dietary lead, there is a larger degree of variability in results of the various water lead studies. The relationship is curvilinear, but its exact form is yet to be determined. At typical levels for U.S. populations, the relationship appears linear. The only study that determines the relationship based on lower water lead values (<100 µg/l) is the Pocock et al. (1983) study. The data from this study, as well as the authors themselves, suggest that in this lower range of water lead levels, the relationship is linear. Furthermore, the estimated contributions to blood lead levels from this study are quite consistent with the polynomial models from other studies. For these reasons, the Pocock et al. (1983) slope of 0.06 is considered to represent the best estimate. The possibility still exists, however, that the higher estimates of the other studies may be correct in certain situations, especially at higher water lead levels (>100 µg/l).

Studies relating soil lead to blood lead levels are difficult to compare. The relationship obviously depends on depth of soil lead, age of the children, sampling method, cleanliness of the home, mouthing activities of the children, and possibly many other factors. Various soil sampling methods and sampling depths have been used over time, and as such they may not be directly comparable and may produce a dilution effect of the major lead concentration contribution from dust which is located primarily in the top 2 cm of the soil. Increases in soil dust lead significantly increase blood lead in children. From several studies (Yankel et al., 1977; Angle and McIntire, 1979) EPA estimates an increase of 0.6-6.8 µg/dl in blood lead for each increase of 1000 µg/g in soil lead concentration. Values of about 2.0 µg/dl per 1,000 µg/g soil lead from the Stark et al. (1982) study may represent a reasonable median estimate. The relationship of housedust lead to blood lead is difficult to obtain. Household dust also increases blood lead, as children from the cleanest homes in the Silver Valley/Kellogg Study had 6 µg/dl less lead in blood, on average, than those from the households with the most dust.

A number of specific environmental sources of airborne lead have been identified as having a direct influence on blood lead levels. Primary lead smelters, secondary lead smelters, and battery plants emit lead directly into the air and ultimately increase soil and dust lead concentrations in their vicinity. Adults, and especially children, have been shown to exhibit elevated blood lead levels when living close to these sources. Blood lead levels in these residents have been shown to be related to air, as well as to soil or dust exposures. The habit of cigarette smoking is a source of lead exposure. Other sources include the following: lead based cosmetics, lead-based folk remedies, and glazed pottery.

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APPENDIX 11A
COMPARTMENTAL ANALYSIS

Many authors have noted that under conditions of constant lead exposure, blood lead concentrations change from one level to another apparent equilibrium level over a period of several months. A mathematical model is helpful in estimating the new apparent equilibrium level even when the duration of the experiment is not sufficiently long for this equilibrium level to have been achieved. The model assumes that lead in the body is held in some number of homogeneous and well-mixed pools or compartments. The compartments have similar kinetic properties and may or may not correspond to identifiable organ systems. In a linear kinetic model it is assumed that the rate of change of the mass of lead in compartment i at time t, denoted $X_i(t)$, is a linear function of the mass of lead in each compartment. Denote the fractional rate of transfer of lead into compartment i from compartment j by K_{ij} (fraction per day), and let $I_i(t)$ be the total external lead input into compartment i at time t in units such as µg/day. The elimination rate from compartment i is denoted K_{0i}. The compartmental model is

$$dX_i(t)/dt = I_i(t) + K_{i1}\,X_1(t) + \cdot\cdot\cdot + K_{in}X_n(t) - (K_{0i} + K_{1i} + \cdot\cdot\cdot + K_{ni})X_i(t)$$

for each of the n compartments. If the inputs are all constant, then each $X_i(t)$ is the sum of (at most) n exponential functions of time (see for example, Jacquez, 1972).

For the one-compartment model

$$dX_i(t)/dt = I_1 - K_{01}\,X_1(t) \qquad (11\text{-}24)$$

with an initial lead burden $X_1(0)$ at time 0,

$$X_1(t) = X_1(0)\,\exp(-K_{01}t) + [(I_1/K_{01})\,(1-\exp(-K_{01}t))] \qquad (11\text{-}25)$$

The mass of lead at equilibrium is I_1/K_{01} µg. We may think of this pool as "blood lead". If the pool has volume V_1 then the equilibrium concentration is $I_1/K_{01}\ V_1$ µg/dl. Intake from several pathways will have the form

$$I_1 = A_1\,(\text{Pb-Air}) + A_2\,(\text{Pb-Diet}) + \cdot\cdot\cdot \qquad (11\text{-}26)$$

so that the long-term concentration is

$$I_1/K_{01}\ V_1 = (A_1/K_{01}V_1)\ \text{Pb-Air} + \cdots \qquad (11\text{-}27)$$

The inhalation coefficient is $\beta = A_1/K_{01}V_1$. The blood lead half-life is $0.693/K_{01}$.

Models with two or more compartments will still have equilibrium concentrations in blood and other compartments that are proportional to the total lead intake, and thus increase linearly with increasing concentrations in air, dust, and diet. The relationship between the exponential parameters and the fractional transfer coefficients will be much more complicated, however.

Models with two or three pools have been fitted by Rabinowitz et al. (1976, 1977) and by Batschelet et al. (1979). The pools are tentatively identified as mainly blood, soft tissue and bone. But as noted in Section 11.4.1.1, the "blood" pool is much larger than the volume of blood itself, and so it is convenient to think of this as the effective volume of distribution for pool 1. A five-pool model has been proposed by Bernard (1977), whose pools are mainly blood, liver, kidney, soft bones and hard bone.

The major conclusion of this Appendix is that linear kinetic mechanisms imply linear relationships between blood lead and lead concentrations in environmental media. An extended discussion of nonlinear kinetic mechanisms is given in Chapter 10, based on analyses in Marcus (1985). One important mechanism involves an apparent limitation on the amount of lead that can be absorbed by the red blood cells. However, at blood lead levels <30 µg/dl this limitation does not greatly affect the linearity of the relationship between blood lead and lead exposure.

APPENDIX 11B

FITTING CURVES TO BLOOD LEAD DATA

The relationship between blood lead and the concentrations of lead in various environmental media is a principal concern of this chapter. It is generally accepted that the geometric mean blood lead is some function, f, of the concentration of air lead and of lead in diet, dust, soil, and other media. It has been observed that blood lead levels have a highly skewed distribution even for populations with relatively homogeneous exposure, and that the variability in blood lead is roughly proportional to the geometric mean blood lead or to the arithmetic mean (constant coefficient of variation). Thus, instead of the usual model in which random variations are normally distributed, a model is assumed here in which the random deviations are multiplicative and lognormally distributed with geometric mean 1 and geometric standard deviation (GSD) e^{σ}. The model is written

$$\text{Pb-Blood} = f\ (\text{Pb-Air, etc.})\ e^{\sigma z} \qquad (11\text{-}28)$$

where z is a random variable with mean 0 and standard deviation 1. It has a Gaussian or normal distribution. The model is fitted to data in logarithmic form

$$\ln(\text{Pb-Blood}) = \ln\ (f) \qquad (11\text{-}29)$$

even when f is assumed to be a linear function, e.g.,

$$f = \beta\ \text{Pb-Air} + \beta_0 + \beta_1\ \text{Pb-Dust} + \ldots \qquad (11\text{-}30)$$

The nonlinear function, fitted by most authors (e.g., Snee, 1982b), is a power function with shape parameter λ,

$$f = (\beta\ \text{Pb-Air} + \beta_0 + \beta_1\ \text{Pb-Dust} + \ldots)^{\lambda} \qquad (11\text{-}31)$$

These functions can all be fitted to data using nonlinear regression techniques. Even when the nonlinear shape parameter λ has a small statistical uncertainty or standard error associated with it, a highly variable data set may not clearly distinguish the linear function ($\lambda = 1$) from a nonlinear function ($\lambda \neq 1$). In particular, for the Azar data set, the residual sum of squares is shown as a function of the shape parameter λ, in Figure 11B-1. When only a

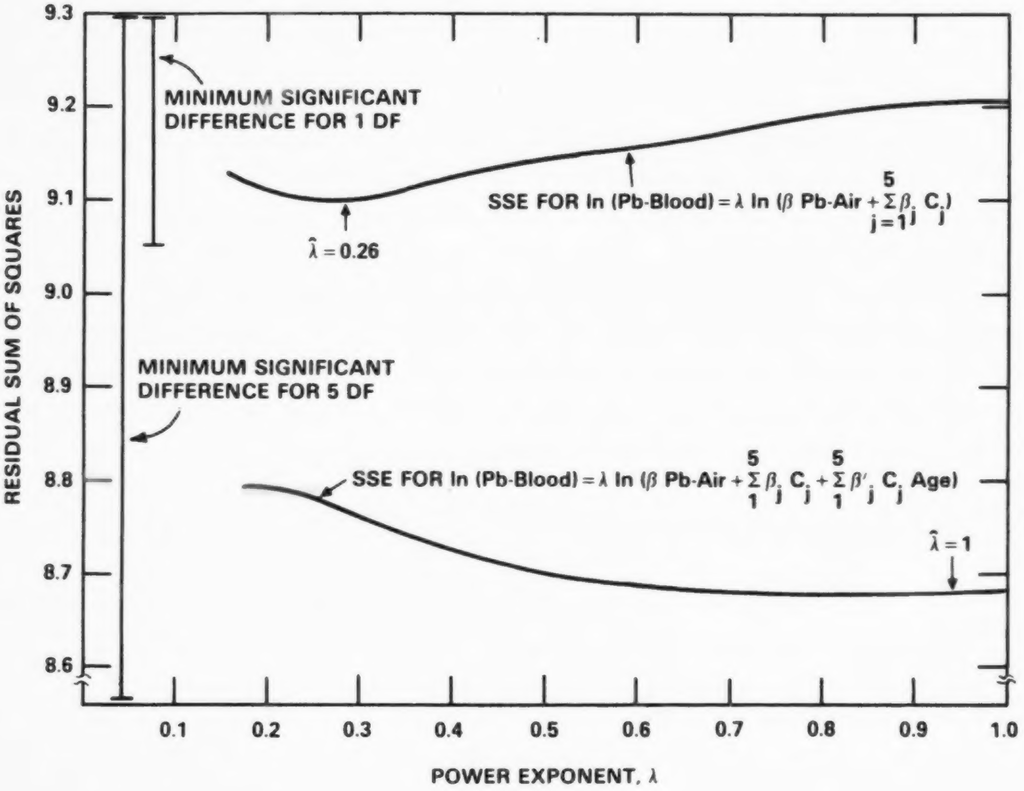

Figure 11 B-1. Residual sum of squares for nonlinear regression models for Azar data (N = 149).

separate intercept (background) is assumed for each subpopulation, the best choice is $\lambda = 0.26$; but when age is also used as a covariate for each subpopulation, then the linear model is better. However, the approximate size of the difference in residual sum of squares required to decide at the 5 percent significance level that a nonlinear model is better (or worse) than a linear model is larger than the observed difference in sum of squares for any $\lambda > 0.2$ (Gallant, 1975). Therefore, a linear model is used unless evidence of nonlinearity is very strong, as with some of Kehoe's studies and the Silver Valley/Kellogg study. Nonlinearity is detectable only when blood lead is high (much above 35 or 40 µg/dl), and intake is high, e.g., air lead much above 10 µg/m^3. Additional research is needed on the relationship between lead levels and lead intake from all environmental pathways.

APPENDIX 11C

ESTIMATION OF GASOLINE LEAD CONTRIBUTIONS TO ADULT BLOOD LEAD BURDENS BASED ON ILE STUDY RESULTS

As discussed in Chapter 11 (pp. 11-118 to 11-123) the results of the Isotopic Lead Experiment (ILE) carried out in Northern Italy provide one basis by which to estimate contributions of lead in gasoline to blood lead burdens of populations exposed in the ILE study area. Figures 11C-1 to 5 of this appendix, reprinted from Facchetti and Geiss (1982), illustrate changes in isotopic $^{206}Pb/^{207}Pb$ ratios for 35 adult subjects, for whom repeated measurements were obtained over time during the ILE study. The percent of total blood lead in those subjects contributed by Australian lead-labeled gasoline (petrol) used in automotive vehicles in the ILE study area was estimated by the approach reprinted below verbatim from Appendix 17 of Facchetti and Geiss (1982):

The main purpose of the ILE project was the determination of the contribution of petrol lead to total lead in blood. A rough value for the fraction of petrol lead in blood can be derived from the following equations:

$$R_1 X + f (1-X) = R' \qquad (1)$$

$$R_2 X + f (1-X) = R'' \qquad (11)$$

each of them referring to a given time at which equilibrium conditions hold.

R' and R'' represent the blood lead isotopic ratios measured at each of the two times; if R_1 and R_2 represent the local petrol lead isotopic ratios measured at the same times, X is the fraction of local petrol lead in blood due to petrols affected by the change in the lead isotopic ratio, irrespective of its pathway to the blood i.e., by inhalation and ingestion (e.g., from petrol lead fallout). The term (1-X) represents the fraction of the sum of all other external sources of lead in the blood (any <<other>> petrol lead included), factor f being the unknown isotopic ratio of the mixture of these sources. It is assumed that X and f remained constant over the period of the experiment, which implies a reasonable constancy of both the lead contributing sources in the test areas and the living habits which, in practice, might not be entirely the case.

Data from individuals sampled at the initial and final equilibrium phases of the ILE study together with petrol lead isotopic ratios measured at the same times, would ideally provide a means to estimate X for Turin and countryside adults. However, for practical reasons, calculations were based on the initial and final data of the subjects whose first sampling was done not later than 1975 and the final one during phase 2. Their complete follow-up data are shown in Table 27. For R_1 and R_2 the values measured in the phases 0 and 2 of ILE were used ($R_1 = 1.186$, $R_2 = 1.060$). Hence, as averages of the individual X and f results, we obtain:

Turin	$X_1 = 0.237 \pm 0.054$ $f_1 = 1.1560 \pm 0.0033$	i.e 24%
countryside <25 km	$X_2 = 0.125 \pm 0.071$ $f_2 = 1.1542 \pm 0.0036$	i.e. 12%
countryside >25 km	$X_3 = 0.110 \pm 0.058$ $f_3 = 1.1576 \pm 0.0019$	i.e 11%

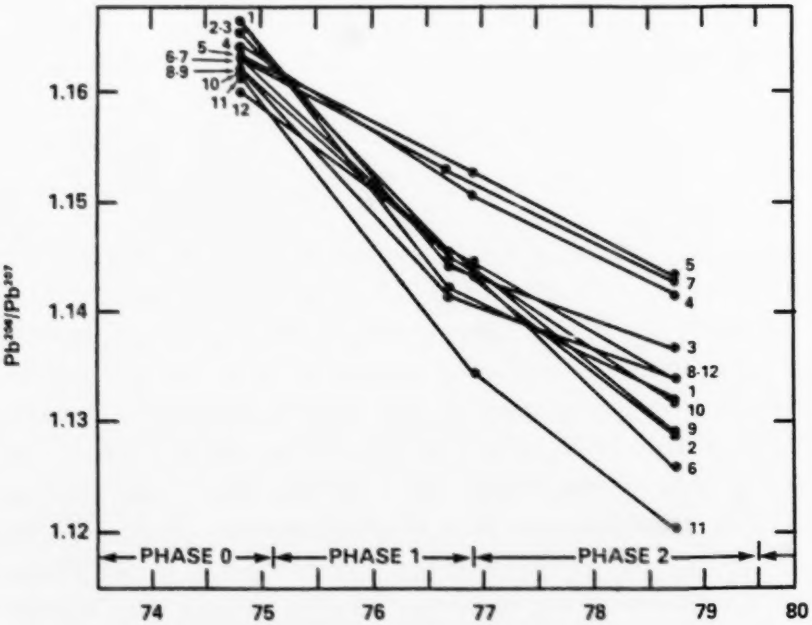

Figure 11C-1. Individual values of blood Pb-206/Pb-207 ratio for subjects follow-up in Turin (12 subjects).

Source: Facchetti and Geiss (1982).

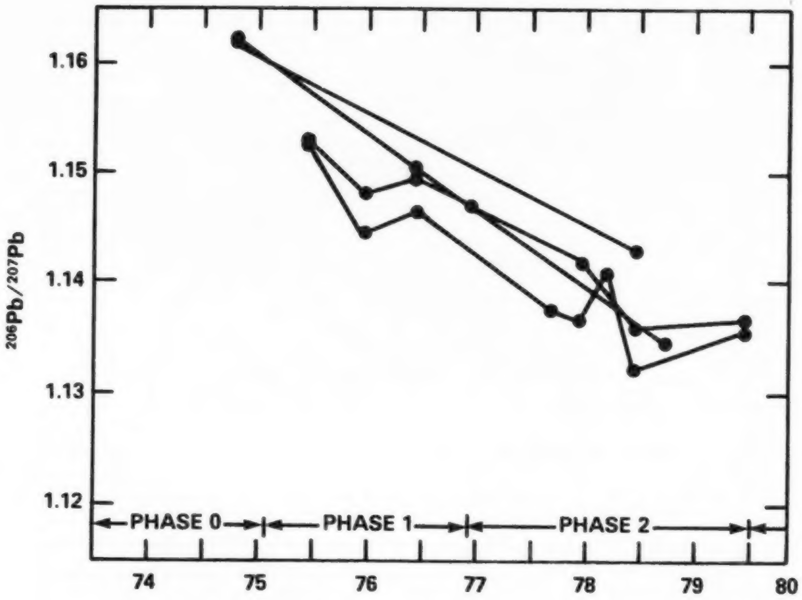

Figure 11C-2. Individual values of blood $^{206}Pb/^{207}Pb$ ratio for subjects follow-up in Castagnetto (4 subjects).

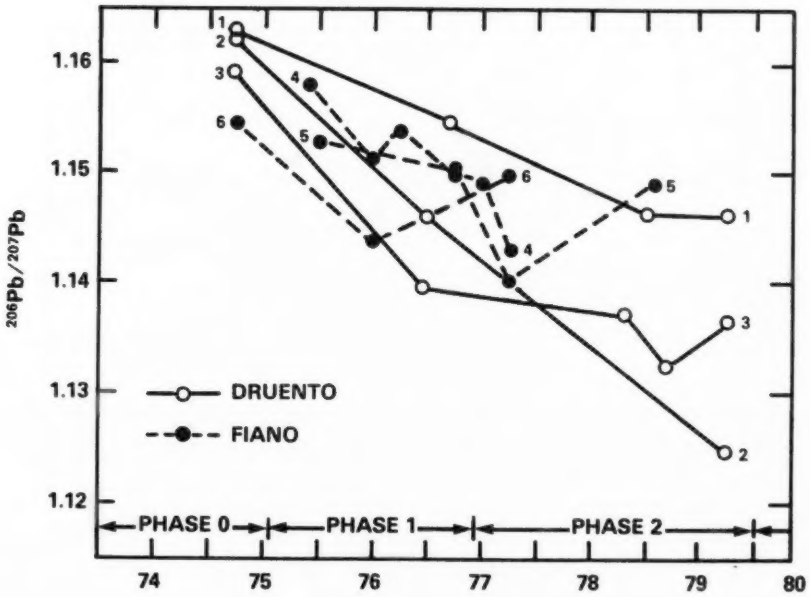

Figure 11C-3. Individual values of blood $^{206}Pb/^{207}Pb$ ratio for subjects follow-up in Druento and Fiano (6 subjects).

Source: Facchetti and Geiss (1982).

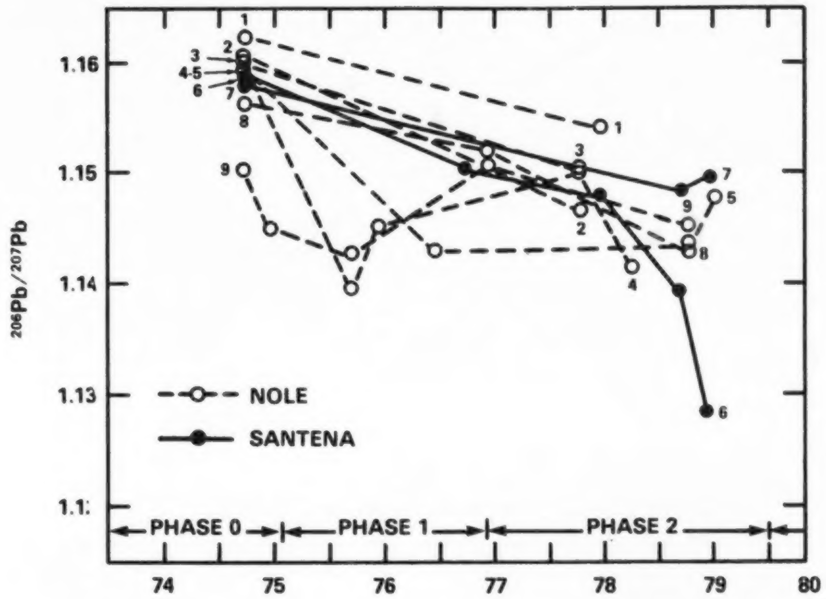

Figure 11C-4. Individual values of blood $^{206}Pb/^{207}Pb$ ratio for subjects follow-up in Nole and Santena (9 subjects).

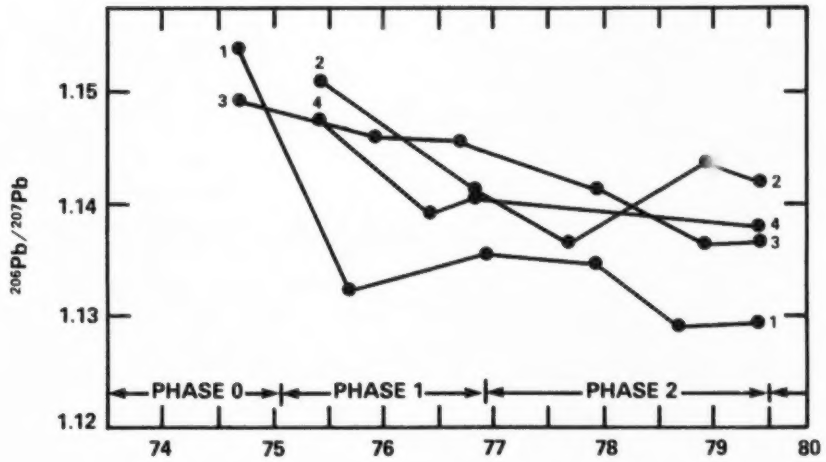

Figure 11C-5. Individual values of blood $^{206}Pb/^{207}Pb$ ratio for subjects follow-up in Viu (4 subjects).

Source: Facchetti and Geiss (1982).

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